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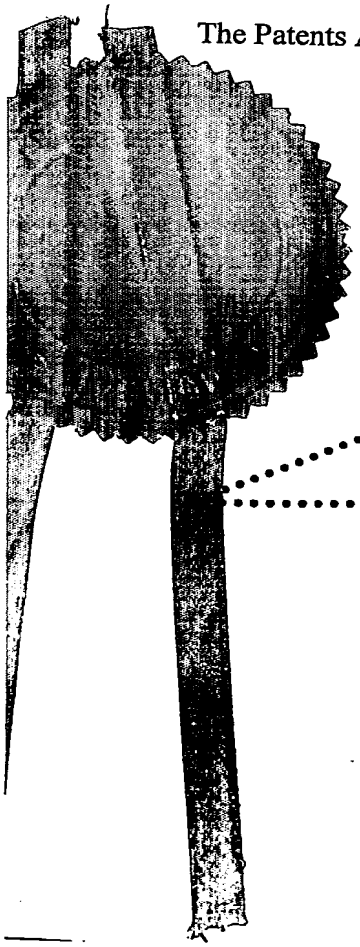
Mumbai – 400 013

IB/04/51922

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annexe is a true copy of Application and Provisional Specification filed on 08/10/2003 in respect of Patent Application No.1054/MUM/2003 of NICHOLAS PIRAMAL INDIA LIMITED, a Company incorporated under the Companies Act, 1956, of 100 Centre Point, Dr. Ambedkar Road, Parel, Mumbai – 400 012, State of Maharashtra, India, An Indian Company.

This certificate is issued under the powers vested in me under Section 14 7 (1) of The Patents Act, 1970.



PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Dated this 15th day of October 2004.

(R.BHATTACHARYA)
ASST.CONTROLLER OF PATENTS & DESIGNS.

WTO

FORM 1

THE PATENTS ACT, 1970
(39 OF 1970)

APPLICATION FOR GRANT OF A PATENT

[See sections 5 (2), 7, 54 and 135 and rule 33A]

1. We (a) NICHOLAS PIRAMAL INDIA LIMITED, (b) a Company incorporated under the Companies Act, 1956, of 100 Centre Point, Dr. Ambedkar Road, Parel, Mumbai - 400 012, State of Maharashtra, India, (c) an Indian company.

2. hereby declare -

(a) that we are in possession of an invention titled " **Fibrinogen receptor antagonists and their use** ".

(b) that the Provisional Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. further declare that the inventors for the said invention are

(a) LAL Bansi, (b) Quest Institute of LifeSciences, Nicholas Piramal India Ltd. Next to Marathon Galaxy, Off L.B.S. Marg, Mulund (W), Mumbai - 400 080, India, (c) an Indian national.

(a) GANGOPADHYAY Ashok Kumar, (b) Quest Institute of LifeSciences, Nicholas Piramal India Ltd., Next to Marathon Galaxy, Off L.B.S. Marg, Mulund (W), Mumbai - 400 080, India, (c) an Indian national.

(a) RAO V.S.V. Vadlamudi, (b) Flat-F6, Vora Towers, 8-3-224, Madhuranagar, Yousufguda Road, Hyderabad-500 038, A.P. India, (c) an Indian national.

(a) GUPTE Ravindra Dattatraya (b) Quest Institute of LifeSciences, Nicholas Piramal India Ltd., Next to Marathon Galaxy, Off L.B.S. Marg, Mulund (W), Mumbai - 400 080, India, (c) an Indian national.

(a) GOLE Gopal Vishnu. (b) Quest Institute of LifeSciences, Nicholas Piramal India Ltd., Next to Marathon Galaxy, Off L.B.S. Marg, Mulund (W), Mumbai - 400 080, India, (c) an Indian national.

(a) KULKARNI-ALMEIDA Asha (b) Quest Institute of LifeSciences, Nicholas Piramal India Ltd., Next to Marathon Galaxy, Off L.B.S. Marg, Mulund (W), Mumbai - 400 080, India, (c) an Indian national.

(a) KRISHNAN Sridevi (b) Quest Institute of LifeSciences, Nicholas Piramal India Ltd., Next to Marathon Galaxy, Off L.B.S. Marg, Mulund (W), Mumbai - 400 080, India, (c) an Indian national

(a) PANICKER Radha Bhaskar (b) Quest Institute of LifeSciences, Nicholas Piramal India Ltd., Next to Marathon Galaxy, Off L.B.S. Marg, Mulund (W), Mumbai - 400 080, India, (c) an Indian national.

(a) PINTO DE SOUZA Eleanor (b) Quest Institute of LifeSciences, Nicholas Piramal India Ltd., Next to Marathon Galaxy, Off L.B.S. Marg, Mulund (W), Mumbai - 400 080, India, (c) an Indian national.

4. We, claim the priority from the application(s) filed in convention countries, particulars of which are as follows:

NONE

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant/patentee:

NOT APPLICABLE

6. I/We state that the application is divided out of my/our application. the particulars of which are given below and pray that this application deemed to have been filed on _____ under section 16 of the Act

NOT APPLICABLE

7. That we are the assignee of the true and first inventors.

8. That our address for service in India is as follows:

NICHOLAS PIRAMAL INDIA LIMITED, Quest Institute Of LifeSciences, Next to Marathon Galaxy, Off L.B.S. Marg, Mulund (W), Mumbai 400 080, State of Maharashtra, India. Phone: 25606960; Fax :25641953.

9. We the true and first inventors for this invention declare that the applicant(s) herein are our assignee.

(a) LAL Bansi
(b) Quest Institute of LifeSciences, Nicholas Piramal India Ltd., Next to Marathon Galaxy, Off L.B.S. Marg, Mulund (W), Mumbai - 400 080, India
(c) An Indian national.

(Bansi Lal)
LAL Bansi

(a) GANGOPADHYAY Ashok Kumar
(b) Quest Institute of LifeSciences, Nicholas Piramal India Ltd., Next to Marathon Galaxy, Off L.B.S. Marg, Mulund (W), Mumbai - 400 080, India
(c) An Indian national.

(A Gangopadhyay)
GANGOPADHYAY Ashok Kumar

(a) RAO V.S.V. Vadlamudi
(b) Flat-F6, Vora Towers, 8-3-224, Madhuranagar, Yousufguda Road, Hyderabad-500 038, A.P. India.
(c) An Indian national.

(V.S.V. Veerabhadra Rao)
RAO V.S.V. Vadlamudi

(a) GUPTE Ravindra Dattatraya.
(b) Quest Institute of LifeSciences, Nicholas Piramal India Ltd., Next to Marathon Galaxy, Off L.B.S. Marg, Mulund (W), Mumbai - 400 080, India.
(c) An Indian national.

( )
GUPTE Ravindra Dattatraya.

(a) GOLE Gopal Vishnu
(b) Quest Institute of LifeSciences, Nicholas Piramal India Ltd., Next to Marathon Galaxy, Off L.B.S. Marg, Mulund (W), Mumbai - 400 080, India,
(c) An Indian national.

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GOLE Gopal Vishnu

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(c) An Indian national.

(_____)
KULKARNI-ALMEIDA Asha

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(b) Quest Institute of LifeSciences, Nicholas Piramal India Ltd., L.B.S. Marg, Mulund (W), Mumbai - 400 080, India,
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(_____)
KRISHNAN Sridevi

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(C) An Indian national.

(_____)
PANICKER Radha Bhaskar

(a) PINTO DE SOUZA Eleanor
(b) Quest Institute of LifeSciences, Nicholas Piramal India Ltd., Next to Marathon Galaxy, Off L.B.S. Marg, Mulund (W), Mumbai - 400 080, India,
(C) An Indian national.

(E. Pinto De Souza)
PINTO DE SOUZA Eleanor

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Following are the attachments with the application:
(a) Provisional specification (3 copies)
(b) Statement and Undertaking on FORM –3 in triplicate.
(c) Fee of Rs. 5,000.00 in cash.
I request that a patent may be granted to us for the said invention.

Dated this 8th day of October, 2003.

Swati Bal-Tembe

Dr. Swati Bal-Tembe
General Manager, Medicinal Chemistry
Head, Patents and Information
NICHOLAS PIRAMAL INDIA LIMITED

To
The Controller of Patents
The Patent Office Branch
At Mumbai

FORM – 2

THE PATENTS ACT, 1970
(39 OF 1970)

PROVISIONAL SPECIFICATION
(See Section 10)

1. TITLE OF THE INVENTION

Fibrinogen Receptor Antagonists And Their Use

2. NICHOLAS PIRAMAL INDIA LIMITED, a company incorporated under the Companies Act, 1956, of 100 Centre Point, Dr. Ambedkar Road, Parel, Mumbai-400 012, State of Maharashtra, India, an Indian company

The following specification describes the nature of the invention

Fibrinogen receptor antagonists and their use

FIELD OF THE INVENTION

The present invention relates to novel compounds, which are antagonists of fibrinogen receptors (FRAs), to pharmaceutical preparations comprising them, to processes for their preparation, and to their use as active ingredients in pharmaceuticals, alone or in combination with other therapeutic agents, in particular for the inhibition of platelet aggregation and for the treatment of thrombotic disorders.

BACKGROUND OF THE INVENTION

Platelets are cell-like anucleated fragments, found in the blood of all mammals that support primary hemostasis by forming hemostatic plugs at sites of vascular injury. Thrombosis is the pathological condition wherein improper activity of the hemostatic mechanism results in intravascular thrombus formation. Activation of platelets and the resulting platelet aggregation has been associated with a variety of pathophysiological conditions including cardiovascular and cerebrovascular thromboembolic disorders, for example, the thromboembolic disorders associated with unstable angina, myocardial infarction, transient ischemic attack, stroke, thrombotic disorders such as peripheral arterial disease, and diabetes.

Glycoprotein IIb/IIIa receptors (hereinafter referred to as GP IIb/IIIa receptors) are found on the surface of platelets and belong to a superfamily of adhesion receptors known as integrins, which are composed of transmembrane glycoproteins containing α and β subunits. Fibrinogen, fibronectin, vitronectin and von Willebrand factor (vWF) are proteins that bind to and crosslink GP IIb/IIIa receptors on adjacent activated platelets and thereby effect aggregation of platelets.

The binding of fibrinogen is mediated in part by the Arginine-Glycine-Aspartic acid (RGD) recognition sequence which is common to the adhesive proteins that bind GP IIb/IIIa receptors (Ferguson, J. J. and Zaqqa, M., Drugs, 1999, 58, 965 – [illegible]; Mousa, S. A and Bennett, J. S., Drugs of the future 1996, 21, 1141 – 1154; Ojima, I., Chakravarty, S. and Dong, Q., Bioorganic and Medicinal Chemistry 1995, 3, 337 – 360).

Platelets are activated by a number of agonists that include adenosine diphosphate (ADP), thrombin, serotonin, arachidonic acid, collagen and adrenaline among others, which are released in the body as a result of various physiological reactions. Regardless of the nature of the stimuli involved in the activation of platelets, the final step of platelet aggregation is the binding of fibrinogen to the activated GP IIb/IIIa receptors on the surface of platelets thereby cross-linking platelets. (J. Lefkovits, E. F. Plow, E. J. Topol 1995, New England Journal of Medicine, 332, 1553-1559). This makes GP IIb/IIIa receptors ideal targets for inhibiting platelet aggregation. The development of GP IIb/IIIa receptor antagonists would, therefore, provide an effective strategy for the control of platelet aggregation and hence thrombi formation (Bennett, J. S, Annual Reviews of Medicine, 2001, 52, 161 - 184).

Cardiovascular diseases are among those that cause the highest mortality throughout the world. Thus, in order to prevent the cardiovascular diseases caused by platelet aggregation, there is an increased necessity for efficient anti-platelet aggregating treatment with drugs possessing specific characteristics namely efficacy, negligible side effects and fast onset of action.

Current antiplatelet drugs are effective against only one type of agonist; these include aspirin, which acts against arachidonic acid; ticlopidine, which acts against ADP; and hirudin, which acts against thrombin.

Until recently, aspirin has been widely used as an inhibitor of platelet function (New England Journal of Medicine, 1994, 330, 1287). While the benefits of aspirin have been demonstrated, there are clinical limitations of this drug. These limitations have provided the impetus for the development of newer antithrombotic agents having therapeutic advantages over aspirin.

Ticlopidine, a thienopyridine derivative, has also been effectively used in patients suffering cardiovascular diseases. However, this drug is associated with a number of serious side effects.

Recently, a common pathway for all known agonists has been identified, namely the platelet GP IIb/IIIa complex, which is the membrane protein mediating platelet aggregation (Phillips et al. Cell 1991, 65, 359-362). The development of GP IIb/IIIa receptor antagonists represents a promising new approach for antiplatelet therapy.

A fibrinogen receptor antagonist (hereinafter referred to as FRA) is an agent that inhibits the binding of fibrinogen to the platelet bound fibrinogen receptor GP IIb/IIIa and thereby prevents platelet aggregation and thrombus formation. Inhibition of platelet aggregation is a major target for the prevention and treatment of cardiovascular diseases.

Known fibrinogen receptor antagonists are:

1. Monoclonal antibodies - e.g. abciximab
2. Parenteral compounds
    a) Synthetic peptides - e.g. eptifibatide
    b) Nonpeptide mimetics - e.g. tirofiban
3. Oral compounds - e.g. roxifiban, gantofiban

1. Monoclonal antibodies:

In 1985, a mouse monoclonal antibody against GP IIb/IIIa, known as c7E3, was generated. Subsequently, the Fab fragment of a chimeric human-mouse genetic reconstruction of c7E3 (c7E3 Fab), known as abciximab, was used in clinical trials (Drugs of the Future, 1995, 20, 457 - 463). Abciximab was launched in 1995 on the US market, as an intravenous preparation.

2. Parenteral compounds:

a) Eptifibatide, a synthetic cyclic peptide (J. Med. Chemistry, 2000, 43, 3453-3473) was designed as a mimic of a snake venom peptide namely barbourin. Eptifibatide is effectively used for the inhibition of platelet aggregation.

b) Based on the observation that peptides containing the tripeptide Arginine-Glycine-Aspartic acid (RGD) sequence function as fibrinogen receptor antagonists, scientists attempted the development of non-peptide mimetics as inhibitors of platelet aggregation (Hartman et.al. J. Med. Chemistry 1992, 35, 4640-4642).

A number of non-peptide fibrinogen receptor antagonists are known and are disclosed in the patents and other publications, which follow:

JP 10-0174 discloses oxyisoindole derivatives possessing fibrinogen receptor antagonistic activity.

EP-A-712844 discloses condensed ring carboxylic acid compounds having platelet GP IIb/IIIa receptor antagonist activity that are useful for the prophylaxis and treatment of thrombotic diseases.

EP-A-540334 discloses isoindolinone compounds as fibrinogen receptor antagonists, which are used in inhibiting the binding of fibrinogen to blood platelets and for inhibiting the aggregation of blood platelets.

WO 96/26187 discloses a series of 3,4-dihydro-1(1*H*)-isoquinolinone based compounds as fibrinogen receptor antagonists useful for inhibiting platelet aggregation with oral activity .

Tirofiban, a non-peptide antagonist, developed by Merck & Co. is the first agent of this class to be used for the treatment of cardiovascular diseases (Hartman G. D. et. al., J. Med. Chemistry, 1992, 35, 4640-4642).

US-A-5 726 185 describes acetic acid derivatives useful for the treatment or prophylaxis of illnesses which are caused by the binding of adhesive proteins to blood platelets and by blood platelet aggregation and cell-cell adhesion.

US-A-5 378 712 describes N-acyl-alpha-aminocarboxylic acid derivatives and N-acyl-alpha-amino acid derivatives which are useful for the treatment or control of illnesses which are caused by the binding of adhesive proteins to blood platelets and by blood platelet aggregation and cell-cell adhesion.

WO 93/07867 discloses substituted beta amino acid derivatives as platelet aggregation inhibitors.

3. Oral compounds:

There are currently no oral preparations on the market. Many compounds that had reached Phase III clinical trials had to be withdrawn due to lack of efficacy or adverse effects such as major bleeding episodes and thrombocytopenia.

EP-A-483667 describes cyclic imino derivatives having aggregation inhibiting effects.

WO 95/18619 describes bicyclic fibrinogen antagonists as inhibitors of platelet aggregation.

WO 95/14683 discloses isoxazolines and isoxazoles that are useful as antagonists of the platelet GP IIb/IIIa fibrinogen receptor complex for the inhibition of platelet aggregation, as thrombolytics and/or for the treatment of thromboembolic disorders.

Gantofiban is a platelet GPIIb/IIIa antagonist for the treatment of various thrombotic diseases, such as acute coronary syndromes (J. Gante et al. Bioorganic and Medicinal Chemistry letters, 1996, 6:20, 2425-2430); Cromafiban is an orally active GP IIb/IIIa antagonist, which was being developed by COR Therapeutics as a potential treatment for thromboembolic disorders, acute coronary syndromes and stroke (Scarborough R.M., et.al, J Med.Chemistry, 2000, 43:19, 3453-3473).

Even though several FRAs are described in the prior art, there is still a need to develop specific agents having fibrinogen receptor antagonistic activity in the advent of the increased mortality rate among patients suffering from cardiovascular diseases.

The FRAs currently available are all intravenous preparations, limiting their use to a hospital environment. A clear clinical need and market exists for FRAs that can be administered by more patient-compliant routes.

A focussed research on FRAs by the present inventors has resulted in the discovery of novel compounds. These compounds are effective inhibitors of GP IIb/IIIa receptors. Moreover, the compounds of the invention inhibit GP IIb/IIIa receptors with an efficacy comparable to the known FRAs, which are under clinical trials. Therefore, the compounds of the present invention are candidate agents for the treatment of thrombotic diseases.

SUMMARY OF INVENTION

It is therefore a principle objective of the present invention to provide novel compounds of general formula (I) or general formulae (Ia) to (Ih) (as described hereinafter).

It is another objective of the invention to provide processes for the preparation of the compounds of general formula (I) or general formulae (Ia) to (Ih) and intermediates thereof.

It is still another objective of the invention to provide pharmaceutical compositions comprising as an active ingredient, compounds of the general formula (I) or general formulae (Ia) to (Ih), or pharmaceutically acceptable salts or prodrugs thereof, together with a pharmaceutically acceptable carrier, diluent or vehicle.

It is still another further objective of the invention to provide the use of compounds of the general formula (I) or general formulae (Ia) to (Ih), or pharmaceutically acceptable salts or prodrugs thereof for the manufacture of a medicament for the inhibition of platelet aggregation in a mammal.

Accordingly, the present compounds can be used for the prevention or treatment of cardiovascular diseases, such as unstable angina, myocardial infarction and stroke, and thrombotic diseases in mammals, especially humans, where antagonism of the binding of fibrinogen to the platelet membrane glycoprotein complex GP IIb/IIIa receptor is desired.

These and other objectives and advantages of the present invention will be apparent to those skilled in the art from the following description.

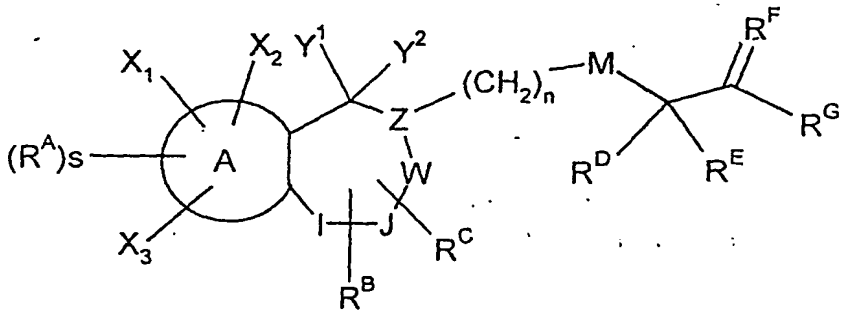
BRIEF DESCRIPTION OF THE DRAWINGS OF THE INVENTION

Figures A to H, J and K represent schemes of preferred processes for the preparation of example compounds of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention discloses novel compounds that inhibit platelet aggregation. The compounds of the present invention are believed to inhibit the binding of fibrinogen to the platelet-bound fibrinogen receptor GP IIb/IIIa and find use in antithrombotic therapies for diseases such as cardiovascular (arterial and/or venous) and cerebrovascular thromboembolic diseases.

The compounds of the present invention are compounds of the general formula (I), prodrugs, tautomeric forms, stereoisomers, pharmaceutically acceptable salts, pharmaceutically acceptable solvates or polymorphs thereof:



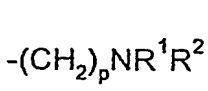
(I)

wherein:

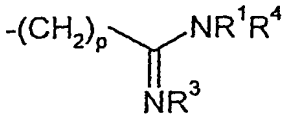
ring A is selected from: aryl and 5-6 membered heteroaryl;

R^A is selected from: $-NO_2$, -CN, $-C(=O)-NR^1R^2$, $-C(=S)NR^1R^2$, $-C(=NR^1)$-SMe and $-C(=NR^1)$-OMe , or

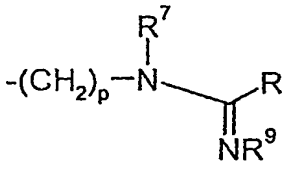
R^A is selected from one of the following groups of formula 2, formula 3 or formula 4:



Formula 2



Formula 3



Formula 4

wherein p is 0, 1, 2, 3, 4 or 5;

s is 1, 2 or 3, and when s is 2 or 3 the groups R^A are independent of each other and can be the same or different;

R^1 and R^2, which are independent of each other and can be the same or different, are selected from: H, C_1-C_{15} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{15} alkenyl, C_2-C_{15} alkynyl, C_3-C_{15} cycloalkyl, C_4-C_{15} cycloalkylalkyl, monocyclic or polycyclic aryl, C_7-C_{17} arylalkyl and C_3-C_{15} heterocycle; or

R^1 and R^2, together with the nitrogen atom to which they are attached, form a saturated, partially saturated, or aromatic heterocycle which optionally contains at least one additional hetero atom selected from: N, O and S;

R^3 and R^4 , which are independent of each other and can be the same or different, are selected from: H, R^1 or R^2, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-S(=O)_2NR^5R^6$, $-S(=O)_2R^5$, $-C(=O)R^5$, $-C(=O)NR^5R^6$, $-C(=O)OR^5$, $-C(=O)SR^5$, $OC(=O)R^5$, $OC(=O)OR^5$, $OC(=O)NR^5R^6$, $OS(=O)_2R^5$, $S(C=O)NR^5$ and $OS(=O)_2NR^5R^6$, wherein R^5 and R^6 , which are independent of each other and can be the same or different, are selected from: H, C_1-C_{15} alkyl, C_2-C_{15} alkenyl, C_2-C_{15}alkynyl, C_3-C_{15} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{17} arylalkyl, and C_3-C_{15} heterocycle, and wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkylalkyl group may contain at least one hetero atom selected from: N, S and O anywhere in the chain, including the terminal position, or

R^3 and R^4, together with the respective nitrogen atoms to which they are attached, form a 5-7 membered partially saturated or aromatic heterocycle;

R^7 and R^9 are interchangeable and have the same meaning as R^3 and R^4, defined above;

R^8 is selected from: H, C_1-C_{15} alkyl, C_2-C_{15} alkenyl, C_2-C_{15} alkynyl, C_3-C_{15} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{17} arylalkyl, and C_3-C_{15} heterocycle, wherein said heterocycle is saturated, partially saturated or aromatic and contains at least one hetero atom selected from: N, O and S, with its point of attachment either through C or N; and wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkylalkyl groups optionally contain at least one hetero atom selected from: N, O and S anywhere in the chain, including the terminal position;

X_1, X_2 and X_3 are members of the ring A, which are independent of each other and can be the same or different, selected from: N, O, S and C-X, wherein X is selected from: H, C_1-C_{13} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{15} alkenyl, C_2-C_{15} alkynyl, C_3-C_{15} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{17} arylalkyl, and C_3-C_{15} heterocycle, or X is an atom or group selected from: -F, -Cl, -Br, -I, -CN, -NC $-NO_2$, $-NR^{10}R^{11}$, $-OR^{10}$, $-SR^{10}$, $S(O)R^{10}$, $S(O)_2R^{10}$, $-NHC(=O)R^{10}$, $-NHOR^{10}$, $-OC(=O)R^{10}$, $-SC(=O)R^{10}$, $-NHC(=O)OR^{10}$, $-OC(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, $-C(=O)R^{10}$, and $-C(=O)OR^{10}$, wherein R^{10} and R^{11} have the same meaning as R^5 or R^6, defined above;

Y^1 and Y^2, which are independent of each other and can be the same or different, are selected from: H, R^{12}, R^{13}, $NR^{12}R^{13}$, OR^{12}, SR^{12}, $CH(OR^{12})$, $CH(SR^{12})$, $CHS(=O)R^{12}$ and $CHS(=O)_2R^{12}$, or

Y^1 and Y^2, together, are selected from: =O, =S, $=CR^{12}R^{13}$, $=NR^{12}$ and $=N\text{-}OR^{12}$,

wherein R^{12} and R^{13} are selected from: H, OR^5, C_1-C_{11} alkyl, C_2-C_{11} alkenyl, C_2-C_{11} alkynyl, C_3-C_{11} cycloalkyl, C_4-C_{13} cycloalkylalkyl and C_6-C_{15} aryl;

Z is selected from: CH, =C and N;

at least one of the ring members I, J and W is present, and I, J and W, which are independent of each other and can be the same or different, are selected from: CR^BR^C, O and N, or

I, J and W, together, are C_1-C_3 alkylene or C_2-C_3 alkenylene, optionally containing at least one hetero atom selected from: O, N and S, wherein at least one ring member is optionally substituted by at least one of R^B and R^C;

R^B and R^C , which are independent of each other and can be the same or different, are selected from: R^5, =O, $=NR^{14}$, =S, CN, $NR^{14}R^{15}$, OR^{14}, SR^{14}, $S(=O)_2R^{16}$ and COR^{16}, wherein R^{14} and R^{15} have the same meaning as R^5 or R^6, defined above;

R^{16} is selected from: H, OR^{14}, $N(R^{14})_2$, $NR^{14}R^{15}$, SR^{14} and R^5, wherein R^5, R^{14} and R^{15} are defined above;

n is 0, 1, 2, 3, 4 or 5;

M is either absent or selected from: –O-, -S-, -S(=O)-, $-S(=O)_2-$, $S(=O)_2NR^{17}$, $-NR^{17}$, -C(=O)-, $-C_1$-C_{10} alkylene, C_2-C_{10} alkenylene, C_6-C_{15} arylphenylene and C_3-C_{15} heterocycle;

R^D and R^E , which are independent of each other and can be the same or different, are selected from: H, C_1-C_{15} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{15} alkenyl, C_2-C_{15} alkynyl, C_3-C_{15} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{17} arylalkyl and C_3-C_{15} heterocycle, where the C_1-C_{15} alkyl optionally contains at least one hetero atom selected from: O, S, and N, and

the C_1-C_{15} alkyl is optionally substituted with at least one functional group selected from: $-OR^{17}$, $-SR^{17}$, $-NR^{17}R^{18}$, $-NHC(=O)R^{17}$, $-NHC(=O)OR^{17}$, $-OC(=O)R^{17}$, $-SC(=O)R^{17}$, $-OS(=O)_2R^{17}$ and $-NHS(=O)_2R^{17}$, wherein R^{17} and R^{18} have the same meaning as R^5 and R^6, defined above, or

when n is 0 and M is absent, one of the groups R^D or R^E is H, and the other is the side chain of an amino acid, the amino acid being either in its natural S configuration, unnatural R configuration, or as a racemic mixture;

R^F is selected from: (H, H), (-H, -OH), O, S, $N(OR^{19})$, $N[OC(=O)OR^{19}]$, $N[OC(=O)R^{19}]$ and $N[OS(=O)_2NR^{19}R^{20}]$, wherein R^{19} and R^{20} have the same meaning as R^5 and R^6 , defined above;

R^G is selected from: mono or polycyclic aryl, heteroaryl, and partially or fully saturated heterocyclic ring, substituted in each case by at least one group independently selected from: $-R^5$, -F, -Cl, -Br, -I, -CN, -SCN, -CNO, $-OR^{21}$, $-OC(=O)R^{21}$, $-OS(=O)_2R^{21}$, $-OS(=O)_2NR^{21}R^{22}$, $-OC(=O)OR^{21}$, $-OC(=O)SR^{21}$, $-OC(=O)\ NR^{21}R^{22}$, $-SR^{21}$, $-S(=O)R^{21}$, $-S(=O)_2R^{21}$, -SC(=O)H, $-SC(=O)OR^{21}$, $-NO_2$, $-NR^{21}(OR^{22})$, $-NR^{21}R^{22}$, $-NR^{21}C(=O)R^{22}$, $-N(R^{21})C(=O)OR^{22}$, $-NR^{21}S(=O)_2R^{22}$, $-N[S(=O)_2R^{21}]\ R^{22}$, $C(=O)OR^{21}$, $-S(=O)_2R^{21}$, $-S(=O)_2OR^{21}$, wherein R^{21} and R^{22} have the same meaning as R^1 or R^2 , defined above , and a group of the following formula 5;

$$T\text{-}(CH_2)_q\text{-}CR^{23}R^{24}\text{-}COR^{25} \qquad \text{(Formula 5)}$$

wherein

T is selected from: $-CH_2$, O, S and N;

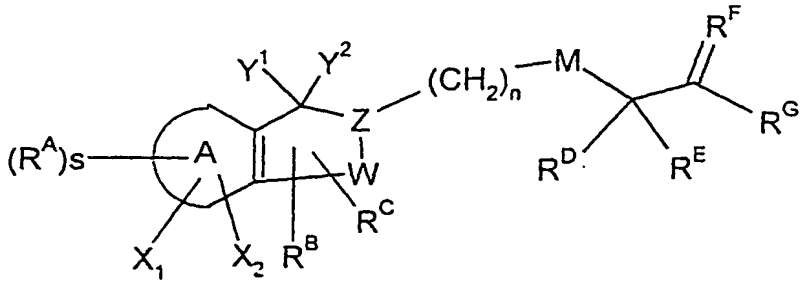
q is 0, 1, 2, 3. 4, 5 or 6 ;

R^{23} and R^{24}, which are independent of each other and can be the same or different, are selected from: R^5, $C(=O)R^{25}$, C_1-C_{15} alkyl and C_2-C_{15} alkenyl, wherein said alkyl and alkenyl contain at least one hetero atom selected from: O, S and N, in any position of the alkyl or alkenyl chain, or said alkyl or alkenyl is substituted with at least one group selected from: $-OR^1$, $-OC(=O)R^1$, $-OS(=O)_2R^1$, $-S(=O)_2NR^1R^2$, $-OC(=O)OR^1$, $-OC(=O)SR^1$, $-OC(=O)NR^1R^2$, $-SR^1$, $-S(=O)R^1$, $-S(=O)_2R^1$, $-SC(=O)H$, $-SC(=O)OR^1$, $-NR^1(OR^2)$, $-NR^1R^2$, $-NR^1C(=O)R^2$, $-N(R^1)C(=O)OR^2$, $-NR^1S(=O)_2R^2$, $-NR^1[S(=O)_2R^2]$, $C(=O)OR^1$, $-S(=O)_2R^1$ and $-S(=O)_2OR^1$;

R^{25} is selected from: OR^5, SR^5 and $-NR^5R^6$, where the group NR^5R^6 is, optionally, a heterocyclic ring which may contain at least one additional heteroatom selected from: O, S, and N;

including racemic, R and S configurations of the compounds, as well as geometrical E/Z or syn/anti isomers, arising from any asymmetric center in the compounds.

In a first embodiment of the invention, there are provided novel compounds of the general formula (Ia), or prodrugs, tautomeric forms, stereoisomers, pharmaceutically acceptable salts, pharmaceutically acceptable solvates, or polymorphs thereof:



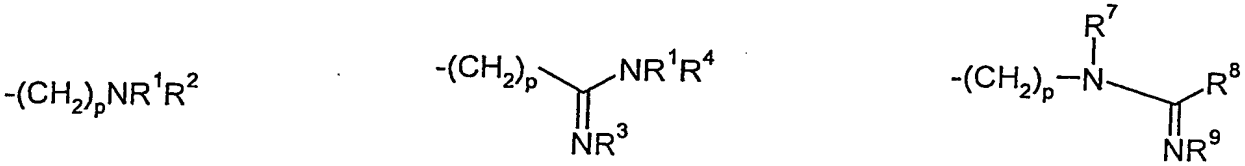
(Ia)

wherein

ring A is selected from: aryl and 5-6 membered heteroaryl;

R^A is selected from: $-NO_2$, -CN, $-C(=O)-NR^1R^2$, $-C(=S)NR^1R^2$, $-C(=NR^1)-SMe$ and $-C(=NR^1)-OMe$; or

R^A is selected from one of the following groups of formula 2, formula 3 or formula 4;



Formula 2 Formula 3 Formula 4

wherein p is 0, 1, 2, 3, 4 or 5;

s is 1, 2 or 3, and when s is 2 or 3 the groups R^A are independent of each other and can be the same or different;

R^1 and R^2 , which are independent of each other and can be the same or different, are selected from: H, C_1-C_{15} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{15} alkenyl, C_2-C_{15} alkynyl, C_3-C_{15} cycloalkyl, C_4-C_{15} cycloalkylalkyl, monocyclic or polycyclic aryl, C_7-C_{17} arylalkyl and C_3-C_{15} heterocycle; or

R^1 and R^2, together with the nitrogen atom to which they are attached, form a saturated, partially saturated or aromatic heterocycle, which optionally contains at least one additional hetero atom selected from: N, O and S;

R^3 and R^4 , which are independent of each other and can be the same or different, are selected from: H, R^1 or R^2, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-S(=O)_2NR^5R^6$, $-S(=O)_2R^5$, $-C(=O)R^5$, $-C(=O)NR^5R^6$, $-C(=O)OR^5$, $-C(=O)SR^5$, $OC(=O)R^5$,

$OC(=O)OR^5$, $OC(=O)NR^5R^6$, $OS(=O)_2R^5$ and $S(=O)_2NR^5R^6$, wherein R^5 and R^6, which are independent of each other and can be the same or different, are selected from: H, C_1-C_{15} alkyl, C_2-C_{15} alkenyl, C_2-C_{15} alkynyl, C_3-C_{15} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{15} arylalkyl and C_3-C_{15} heterocycle, and wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkylalkyl group optionally contains at least one hetero atom selected from: N, O and S, anywhere in the chain, including the terminal position, or

R^3 and R^4, together with the respective nitrogen atoms to which they are attached, form a 5-7 membered partially saturated or aromatic heterocycle;

R^7 and R^9 are interchangeable and have the same meaning as R^3 and R^4, defined above;

R^8 is selected from: H, C_1-C_{15} alkyl, C_2-C_{15} alkenyl, C_2-C_{15} alkynyl, C_3-C_{15} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{17} arylalkyl and C_3-C_{15} heterocycle, wherein said heterocycle is saturated, partially saturated or aromatic and contains at least one hetero atom selected from: N, O and S, with its point of attachment either through C or N, and wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkylalkyl groups optionally contains at least one hetero atom selected from: N, O and S, anywhere in the chain, including the terminal position;

X_1 and X_2 are members of the ring A, which are independent of each other and can be the same or different, and are selected from: N, O, S and C-X, wherein X is selected from: H, C_1-C_{13} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{15} alkenyl, C_2-C_{15} alkynyl, C_3-C_{15} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{17} arylalkyl and C_3-C_{15} heterocycle, or X is an atom or group selected from: -F, -Cl, -Br, -I, -CN, -NC, $-NO_2$; or $-NR^{10}R^{11}$, $-OR^{10}$, $-SR^{10}$, $S(O)R^{10}$, $S(O)_2R^{10}$, $-NHC(=O)R^{10}$, $-NHOR^{10}$, $-OC(=O)R^{10}$, $-SC(=O)R^{10}$, $-NHC(=O)OR^{10}$, -

$OC(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, $-C(=O)R^{10}$ and $-C(=O)OR^{10}$, wherein R^{10} and R^{11} have the same meaning as R^5 or R^6, defined above;

Y^1 and Y^2, which are independent of each other and can be the same or different, are selected from: H, R^{12}, R^{13}, $NR^{12}R^{13}$, OR^{12}, SR^{12}, $CH(OR^{12})$, $CH(SR^{12})$, $CHS(=O)R^{12}$ and $CHS(=O)_2R^{12}$, or
Y^1 and Y^2, together, are selected from: =O, =S, $=CR^{12}R^{13}$, $=NR^{12}$ and $=N\text{-}OR^{12}$, wherein R^{12} and R^{13} , which are independent of each other and can be the same or different, are selected from: C_1-C_{11} alkyl, C_2-C_{11} alkenyl, C_2-C_{11} alkynyl, C_3-C_{11} cycloalkyl, C_4-C_{13} cycloalkylalkyl and C_6-C_{15} aryl;
Z is selected from: CH, =C and N;

W is selected from: CR^BR^C, O and N, or

W is C_1-C_3 alkylene or C_2-C_3alkenylene, optionally containing at least one hetero atom selected from: O, N and S, wherein at least one ring member of W is optionally substituted by at least one of R^B and R^C;

R^B and R^C , which are independent of each other and can be the same or different, are selected from: R^5, =O, $=NR^{14}$, =S, CN, $NR^{14}R^{15}$, OR^{14}, SR^{14}, $S(=O)_2R^{16}$ and COR^{16}, wherein R^{14} and R^{15} have the same meaning as R^5 or R^6, defined above;

R^{16} is selected from: H, OR^{14}, $N(R^{14})_2$, $NR^{14}R^{15}$, SR^{14} and R^5, wherein R^5, R^{14} and R^{15} are defined above;

n is an integer having a value of 0, 1, 2, 3, 4 or 5;

M is either absent or selected from: –O-, -S-, -S(=O)-, $-S(=O)_2$-, $S(=O)_2NR^{17}$, $-NR^{17}$-, -C(=O)-, $-C_1$-C_{10} alkylene, C_2-C_{10} alkenylene, C_6-C_{15} arylphenylene and C_3-C_{15} heterocycle;

R^D and R^E , which are independent of each other and can be the same or different, are selected from: H, C_1-C_{15} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{15} alkenyl, C_2-C_{15} alkynyl, C_3-C_{15} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{17} arylalkyl and C_3-C_{15} heterocycle, where the C_1-C_{15} alkyl optionally contains at least one hetero atom selected from: O, S and N, and the C_1-C_{15} alkyl is optionally substituted with at least one functional group selected from: $-OR^{17}$, $-SR^{17}$, $-NR^{17}R^{18}$, $-NHC(=O)R^{17}$, $-NHC(=O)OR^{17}$, $-OC(=O)R^{17}$, $-SC(=O)R^{17}$, $-OS(=O)_2R^{17}$ and $-NHS(=O)_2R^{17}$, wherein R^{17} and R^{18} have same meaning as R^5 and R^6, defined above; or

when n is 0 and M is absent, optionally one of the groups R^D or R^E is H, and the other is the side chain of an amino acid, the amino acid being either in its natural S configuration, unnatural R configuration or as a racemic mixture;

R^F is selected from: (H, H), (H, OH), O, S, $N(OR^{19})$, $N[OC(=O)OR^{19}]$, $N[OC(=O)R^{19}]$, and $N[OS(=O)_2NR^{19}R^{20}]$, wherein R^{19} and R^{20} have the same meaning as R^5 and R^6 , defined above;

R^G is selected from: mono- or polycyclic aryl, heteroaryl and partially or fully saturated heterocyclic, substituted by at least one group selected from: $-R^5$, -F, -Cl, -Br, -I, -CN, -SCN, -CNO, $-OR^{21}$, $-OC(=O)R^{21}$, $-OS(=O)_2R^{21}$, $-OS(=O)_2NR^{21}R^{22}$, $-OC(=O)OR^{21}$, $-OC(=O)SR^{21}$, $-OC(=O)\ NR^{21}R^{22}$, $-SR^{21}$, $-S(=O)R^{21}$, $-S(=O)_2R^{21}$, -SC(=O)H, $-SC(=O)OR^{21}$, $-NO_2$, $-NR^{21}(OR^{22})$, $-NR^{21}R^{22}$, $-NR^{21}C(=O)R^{22}$, $-N(R^{21})C(=O)OR^{22}$, $-NR^{21}S(=O)_2R^{22}$, $-N[S(=O)_2R^{21}]$, $C(=O)OR^{21}$, $-S(=O)_2R^{21}$, $-S(=O)_2OR^{21}$, wherein R^{21} and R^{22} have the same meaning as R^1 or R^2 , defined above, and a group of the following formula 5;

$$T\text{-}(CH_2)_q\text{-}CR^{23}R^{24}\text{-}COR^{25} \qquad \text{(Formula 5)}$$

wherein

T is selected from: $-CH_2$, O, S and N;

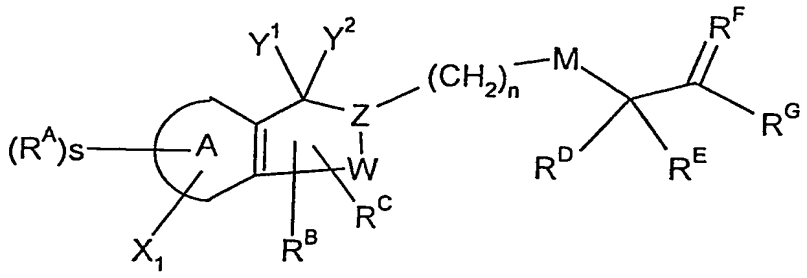
q is 0, 1, 2 or 3;

R^{23} and R^{24} , which are independent of each other and can be the same or different, are selected from: R^5, $C(=O)R^{25}$, (C_1-C_{15}) alkyl and C_2-C_{15} alkenyl, wherein said alkyl and alkenyl chain contains at least one hetero atom selected from: O, S, N, in any position of the alkyl or alkenyl chain, or said alkyl or alkenyl is substituted with at least one group selected from: $-OR^1$, $-OC(=O)R^1$ - $OS(=O)_2R^1$, $-S(=O)_2NR^1R^2$, $-OC(=O)OR^1$, $-OC(=O)SR^1$, $-OC(=O)NR^1R^2$, $-SR^1$, $-S(=O)R^1$, $-S(=O)_2R^1$, $-SC(=O)H$, $-SC(=O)OR^1$, $-NR^1(OR^2)$, $-NR^1R^2$, $-NR^1C(=O)R^2$, $-NR^1C(=O)OR^2$, $-NR^1S(=O)_2R^2$, $-N[S(=O)_2R^1]C(=O)OR^2$, $-S(=O)_2R^1$ and $-S(=O)_2OR^1$;

R^{25} selected from OR^5, SR^5 and $-NR^5R^6$, wherein the group NR^5R^6 is optionally a heterocyclic ring which may contain at least one additional heteroatom selected from: O, S and N;

including racemic, R and S configurations of the compounds, as well as geometrical E/Z or syn/anti isomers, arising from any asymmetric center in the compounds.

In a second embodiment of the invention, there are provided novel compounds of the general formula (Ib), or prodrugs, tautomeric forms, stereoisomers, pharmaceutically acceptable salts, pharmaceutically acceptable solvates or polymorphs thereof:



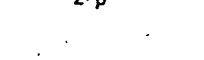
(Ib)

wherein:

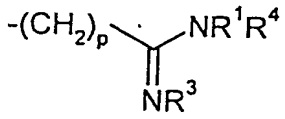
ring A is selected from: aryl and 5-6 membered heteroaryl;

R^A is selected from: $-NO_2$, -CN, $-C(=O)-NR^1R^2$, $-C(=S)NR^1R^2$, $-C(=NR^1)-SMe$ and $-C(=NR^1)-OMe$, or

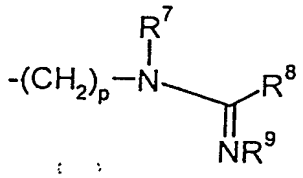
R^A is selected from one of the following groups of formula 2, formula 3 or formula 4;



Formula 2



Formula 3



Formula 4

wherein p is 0, 1 or 2 ;

s is 1, 2 or 3, and when s is 2 or 3 the groups R^A are independent of each other and can be the same or different;

R^1 and R^2 , which are independent of each other and can be the same or different, are selected from: H, C_1-C_{13} alkyl, partially or fully fluorinated C_1-C_{10}

alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{17} arylalkyl and C_3-C_{15} heterocycle, or

R^1 and R^2, together with the nitrogen atom to which they are attached, form a saturated, partially saturated or aromatic heterocycle, which optionally contains at least one additional hetero atom selected from: N, O and S;

R^3 and R^4, which are independent of each other and can be the same or different, are selected from: H, R^1 or R^2, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-S(=O)_2NR^5R^6$, $-S(=O)_2R^5$, $-C(=O)R^5$, $-C(=O)NR^5R^6$, $-C(=O)OR^5$, $-C(=O)SR^5$, $OC(=O)R^5$, $OC(=O)OR^5$, $OC(=O)NR^5R^6$, $OS(=O)_2R^5$ and $OS(=O)_2NR^5R^6$, wherein R^5 and R^6, which are independent of each other and can be the same or different, are selected from: H, C_1-C_{13} alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{17} arylalkyl and C_3-C_{13} heterocycle, and wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkylalkyl groups optionally contain at least one hetero atom selected from: N, O and S, anywhere in the chain, including the terminal position, or

R^3 and R^4, together with the respective nitrogen atoms to which they are attached, form a 5-7 membered partially saturated or aromatic heterocycle;

R^7 and R^9 are interchangeable and have the same meaning as R^3 and R^4, defined above;

R^8 is selected from: H, C_1-C_{13} alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{15} arylalkyl and C_3-C_{13} heterocycle, wherein said heterocycle is saturated, partially saturated or aromatic and contains at least one hetero atom selected from: N, O and S, with its point of attachment either through C or N; and wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkylalkyl groups optionally contains at least

one hetero atom selected from: N, O and S, anywhere in the chain, including the terminal position;

X_1 is a member of the ring A, and is selected from: N, O, S and C-X , wherein X is H, C_1-C_{13} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{15} arylalkyl or C_3-C_{13} heterocycle, or
X is an atom or group, such as selected from: -F, -Cl, -Br, -I, -CN, -NC, -NO_2, -$NR^{10}R^{11}$, -OR^{10}, -SR^{10}, $S(O)R^{10}$, $S(O)_2R^{10}$, -$NHC(=O)R^{10}$, -$NHOR^{10}$, -$OC(=O)R^{10}$, -$SC(=O)R^{10}$, -$NHC(=O)OR^{10}$, -$OC(=O)OR^{10}$, -$C(=O)NR^{10}R^{11}$, -$C(=O)R^{10}$ and -$C(=O)OR^{10}$, wherein R^{10} and R^{11} have the same meaning as R^5 or R^6, defined above;

Y^1 and Y^2, which are independent of each other and can be the same or different, are selected from: H, R^{12}, R^{13}, $NR^{12}R^{13}$, OR^{12}, SR^{12}, $CH(OR^{12})$, or

Y^1 and Y^2, together, are selected from: =O, =S, $=CR^{12}R^{13}$, $=NR^{12}$ and $=N\text{-}OR^{12}$,

wherein R^{12} and R^{13} , which are independent of each other and can be the same or different, are selected from: C_1-C_{11} alkyl, C_2-C_{11} alkenyl, C_2-C_{11} alkynyl, C_3-C_{11} cycloalkyl, C_4-C_{13} cycloalkylalkyl and C_6-C_{13} aryl;

Z is selected from: CH, =C and N;

W is selected from: CR^BR^C, O and N, or

W is C_1-C_3 alkylene or C_2-C_3alkenylene, optionally containing at least one hetero atom selected from: O, N and S and wherein at least one ring member of W is optionally substituted by at least one of R^B and R^C;

R^B and R^C , which are independent of each other and can be the same or different, are selected from: R^5, = O, $=NR^{14}$, =S, CN, $NR^{14}R^{15}$, OR^{14}, SR^{14}, $S(=O)_2R^{16}$ and COR^{16} , wherein R^{14} and R^{15} have the same meaning as R^5 and R^6 , defined above;

R^{16} is selected from: H, OR^{14}, $N(R^{14})_2$, $NR^{14}R^{15}$, $SR^{14}$and R^5, wherein R^5, R^{14} and R^{15} are as defined above;

n is 0, 1, 2, 3, 4 or 5;

M is either absent or is selected from –O-, -S-, -S(=O)-, $-S(=O)_2-$, $-NR^{17}-C(=O)-$, C_1-C_8 alkylene, C_2-C_8 alkenylene, C_6-C_{15} phenylene and C_3-C_{15} heterocycle;

R^D and R^E , which are independent of each other and can be the same or different, are selected from: H, C_1-C_{13} alkyl, partially or fully fluorinated C_1-C_8 alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{13} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{13} aryl, C_7-C_{17} arylalkyl and C_3-C_{13} heterocycle, where the C_1-C_{13} alkyl optionally contains at least one hetero atom selected from: O, S and N, and the C_1-C_{13} alkyl is optionally substituted with at least one functional group selected from: $-OR^{17}$, $-SR^{17}$, $-NR^{17}R^{18}$, $-NHC(=O)R^{17}$, $-NHC(=O)OR^{17}$, $-OC(=O)R^{17}$, $-SC(=O)R^{17}$, $-OS(=O)_2R^{17}$and $-NHS(=O)_2R^{17}$, wherein R^{17} and R^{18} have same meaning as R^5 and R^6 , defined above; or

when n is 0 and M is absent, optionally one of the groups R^D or R^E is H, and the other is the side chain of an amino acid, the amino acid being either in its natural S configuration, unnatural R configuration, or as a racemic mixture;

R^F is selected from: (H, H), (H, OH), O, S, $N(OR^{19})$, $N[OC(=O)OR^{19}]$, $N[OC(=O)R^{19}]$ and $N[OS(=O)_2NR^{19}R^{20}]$, wherein R^{19} and R^{20} have the same meaning as R^5 and R^6 , defined above;

R^G is selected from: mono- or polycyclic aryl, heteroaryl, partially or fully saturated heterocyclic, substituted by at least one group independently selected from: $-R^5$, -F, -Cl, -Br, -I, -CN, $-OR^{21}$, $-OC(=O)R^{21}$, $-OS(=O)_2R^{21}$, $-OS(=O)_2NR^{21}R^{22}$, $-OC(=O)OR^{21}$, $-OC(=O)SR^{21}$, $-OC(=O)\ NR^{21}R^{22}$, $-SR^{21}$, $-S(=O)R^{21}$, $-S(=O)_2R^{21}$, -SC(=O)H, $-SC(=O)OR^{21}$, $-NO_2$, $-NR^{21}(OR^{22})$, $-NR^{21}R^{22}$, $-N(R^{21})C(=O)R^{22}$, $-N(R^{21})C(=O)OR^{22}$, $-NR^{21}S(=O)_2R^{22}$, $-N[S(=O)_2R^{21}]$, $-C(=O)OR^{21}$, $-S(=O)_2R^{21}$ and $-S(=O)_2OR^{21}$, wherein R^{21} and R^{22} have the same meaning as R^1 or R^2 as defined above, and a group of the following formula 5:

$$T\text{-}(CH_2)_q\text{-}CR^{23}R^{24}\text{-}COR^{25} \qquad \text{(Formula 5)}$$

wherein

T is selected from: $-CH_2$, O, S and N;

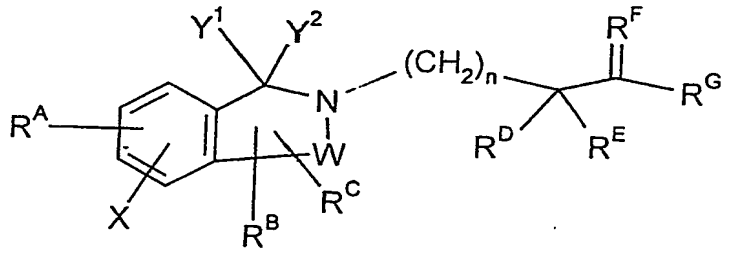
q is 0, 1, 2 or 3;

R^{23} and R^{24} , which are independent of each other and can be the same or different, are selected from: R^5, $C(=O)R^{25}$, $(C_1\text{-}C_{13})$ alkyl, $C_2\text{-}C_{13}$ alkenyl, wherein said alkyl and alkenyl contain at least one hetero atom selected from: O, S and N, in any position of the alkyl or alkenyl chain, or said alkyl or alkenyl is substituted with at least one group selected from: $-OR^1$, $-OC(=O)R^1$, $-OS(=O)_2R^1$, $-S(=O)_2NR^1R^2$, $-OC(=O)OR^1$, $-OC(=O)SR^1$, $-OC(=O)NR^1R^2$, $-SR^1$, $-S(=O)R^1$, $-S(=O)_2R^1$, -SC(=O)H, $-SC(=O)OR^1$, $-NR^1(OR^2)$, $-NR^1R^2$, $-NR^1C(=O)R^2$, $-NR^1C(=O)OR^2$, $-NR^1S(=O)_2R^2$, $-N[S(=O)_2R^1]C(=O)OR^2$, $-S(=O)_2R^1$ and $-S(=O)_2OR^1$;

R^{25} is selected from: OR^5, SR^5 and $-NR^5R^6$, where the group $-NR^5R^6$ is optionally a heterocyclic ring which may contain at least one additional heteroatom selected from: O, S and N;

including racemic, R and S configurations of the compounds, as well as geometrical E/Z or syn/anti isomers, arising from any asymmetric center in the compounds.

In a third embodiment of the invention, there are provided novel compounds of the general formula (Ic), or prodrugs, tautomeric forms, stereoisomers, pharmaceutically acceptable salts, pharmaceutically acceptable solvates or polymorphs thereof;

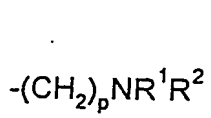


(Ic)

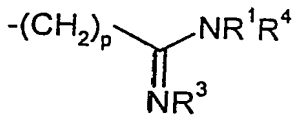
wherein

R^A is selected from: $-NO_2$, -CN, $-C(=O)-NR^1R^2$, $-C(=S)NR^1R^2$, $-C(=NR^1)$-SMe and $-C(=NR^1)$-OMe ; or

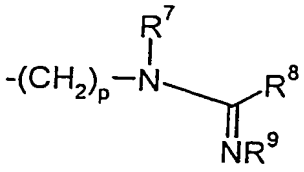
R^A is selected from one of the following groups of formula 2, formula 3 or formula 4;



Formula 2



Formula 3



Formula 4

wherein p is 0, 1 or 2;

R^1 and R^2 , which are independent of each other and can be the same or different, are selected from: H, C_1-C_{13} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{17} arylalkyl and C_3-C_{15} heterocycle, or

R^1 and R^2, together with the nitrogen atom to which they are attached, form a saturated, partially saturated, or aromatic heterocycle which optionally contains at least one additional hetero atom selected from: N, O and S;

R^3 and R^4 , which are independent of each other and can be the same or different, are selected from: H, R^1 or R^2, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-S(=O)_2NR^5R^6$, $-S(=O)_2R^5$, $-C(=O)R^5$, $-C(=O)NR^5R^6$, $-C(=O)OR^5$, $-C(=O)SR^5$, $OC(=O)R^5$, $OC(=O)OR^5$, $OC(=O)NR^5R^6$, $OS(=O)_2R^5$ and $OS(=O)_2NR^5R^6$, wherein R^5 and R^6, which are independent of each other and can be the same or different, are selected from: H, C_1-C_{13} alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{17} arylalkyl and C_3-C_{13} heterocycle, and wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkylalkyl group optionally contains at least one hetero atom selected from: N, O and S, anywhere in the chain, including the terminal position, or

R^3 and R^4, together with the respective nitrogen atoms to which they are attached, form a 5-7 membered partially saturated or aromatic heterocycle;

R^7 and R^9 are interchangeable and have the same meaning as R^3 and R^4, defined above;

R^8 is selected from: H, C_1-C_{13} alkyl. C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{15} arylalkyl and C_3-C_{13} heterocycle, wherein said heterocycle is saturated, partially saturated or aromatic and contains at least one hetero atom selected from: N, O and S; with

its point of attachment either through C or N, and wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkylalkyl groups optionally contain at least one hetero atom selected from: N, O and S, anywhere in the chain, including the terminal position;

X is selected from: H, C_1-C_{13} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{15} arylalkyl and C_3-C_{13} heterocycle, or

X is an atom or group selected from: -F, -Cl, -Br, -I, -CN, -NC, $-NO_2$, $-NR^{10}R^{11}$, $-OR^{10}$, $-SR^{10}$, $S(O)R^{10}$, $S(O)_2R^{10}$, $-NHC(=O)R^{10}$, $-NHOR^{10}$, $-OC(=O)R^{10}$, $-SC(=O)R^{10}$, $-NHC(=O)OR^{10}$, $-OC(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, $-C(=O)R^{10}$ and $-C(=O)OR^{10}$, wherein R^{10} and R^{11} have the same meaning as R^5 or R^6, defined above;

Y^1 and Y^2, which are independent of each other and can be the same or different, are selected from: H, R^{12}, R^{13}, $NR^{12}R^{13}$, OR^{12}, SR^{12} and $CH(OR^{12})$, or

Y^1 and Y^2, together are selected from: =O, =S, $=CR^{12}R^{13}$, $=NR^{12}$ and $=N\text{-}OR^{12}$

wherein R^{12} and R^{13} , which are independent of each other and can be the same or different, are selected from: C_1-C_{11} alkyl, C_2-C_{11} alkenyl, C_2-C_{11} alkynyl, C_3-C_{11} cycloalkyl, C_4-C_{13} cycloalkylalkyl and C_6-C_{13} aryl;

W is selected from CR^BR^C, O and N, or

W is C_1-C_3 alkylene or C_2-C_3 alkenylene, each optionally containing at least one hetero atom selected from: O, N and S, wherein at least one ring member of W is optionally substituted by at least one of R^B and R^C;

R^B and R^C , which are independent of each other and can be the same or different, are selected from: R^5, = O, $=NR^{14}$, =S, CN, $NR^{14}R^{15}$, OR^{14}, SR^{14},

$S(=O)_2R^{16}$ and COR^{16}, wherein R^{14} and R^{15} have the same meaning as R^5 or R^6, defined above;

R^{16} is selected from: H, OR^{14}, $N(R^{14})_2$, $NR^{14}R^{15}$, $SR^{14}$and R^5, wherein R^5, R^{14} and R^{15} are as defined above;

n is 0, 1, 2, 3, 4 or 5;

R^D and R^E , which are independent of each other and can be the same or different, are selected from: H, C_1-C_{13} alkyl, partially or fully fluorinated C_1-C_8 alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{13} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{13} aryl, C_7-C_{17} arylalkyl and C_3-C_{13} heterocycle, where the C_1-C_{13} alkyl optionally contains at least one hetero atom selected from: N, O and S, and the C_1-C_{13} alkyl is optionally substituted with at least one functional group selected from: $-OR^{17}$, $-SR^{17}$, $-NR^{17}R^{18}$, $-NHC(=O)R^{17}$, $-NHC(=O)OR^{17}$, $-OC(=O)R^{17}$, $-SC(=O)R^{17}$, $-OS(=O)_2R^{17}$ and $-NHS(=O)_2R^{17}$, wherein R^{17} and R^{18} have same meaning as R^5 and R^6, defined above, or

when n is 0 and M is absent, optionally one of the groups R^D and R^E is H, and the other is the side chain of an amino acid, the amino acid being either in its natural S configuration, unnatural R configuration or as a racemic mixture;

R^F is selected from: (H, H) (H, OH), O, S, $N(OR^{19})$, $N[OC(=O)OR^{19}]$, $N[OC(=O)R^{19}]$ and $N[OS(=O)_2NR^{19}R^{20}]$, wherein R^{19} and R^{20} have the same meaning as R^5 and R^6, defined above;

R^G is selected from: mono- or polycyclic aryl, heteroaryl, partially or fully saturated heterocyclic, substituted by at least one group selected from: $-R^5$, -F, -Cl, -Br, -I, -CN, -SCN, -CNO, $-OR^{21}$, $-OC(=O)R^{21}$, $-OS(=O)_2R^{21}$, $-OS(=O)_2NR^{21}R^{22}$, $-OC(=O)OR^{21}$, $-OC(=O)SR^{21}$, $-OC(=O)\ NR^{21}R^{22}$, $-SR^{21}$, $-S(=O)R^{21}$, $-S(=O)_2R^{21}$, -SC(=O)H, $-SC(=O)OR^{21}$, $-NO_2$, $-NR^{21}OH$, $-NR^{21}(OR^{22})$, -

$NR^{21}R^{22}$, $-NR^{21}C(=O)R^{22}$, $-N(R^{21})C(=O)OR^{22}$, $-NR^{22}S(=O)_2R^{22}$, $-N[S(=O)_2R^{21}]R^{22}$, $-C(=O)OR^{21}$, $-S(=O)_2R^{21}$, $-S(=O)_2OR^{21}$, wherein R^{21} and R^{22} have the same meaning as R^1 or R^2 as defined above, and a group of the following formula 5;

$$T\text{-}(CH_2)_q\text{-}CR^{23}R^{24}\text{-}COR^{25} \qquad \text{(Formula 5)}$$

wherein

T is selected from: $-CH_2$, O, S and N;

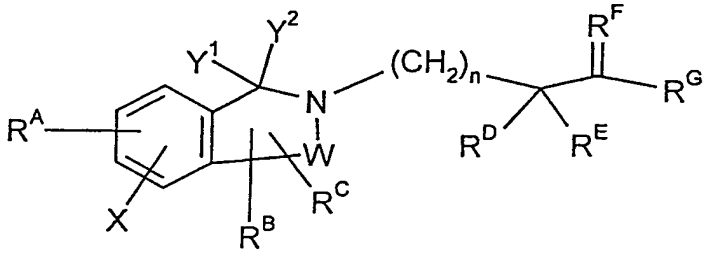
q is 0, 1, 2 or 3;

R^{23} and R^{24} , which are independent of each other and can be the same or different, are selected from: R^5, $C(=O)R^{25}$, C_1-C_{13} alkyl and C_2-C_{13} alkenyl, wherein said alkyl and alkenyl contain at least one hetero atom selected from: O, S and N in any position of the alkyl or alkenyl chain, or said alkyl or alkenyl is substituted with at least one group selected from: $-OR^1$, $-OC(=O)R^1$ $-OS(=O)_2R^1$, $-S(=O)_2NR^1R^2$, $-OC(=O)OR^1$, $-OC(=O)SR^1$, $-OC(=O)\ NR^1R^2$, $-SR^1$, $-S(=O)R^1$, $-S(=O)_2R^1$, $-SC(=O)H$, $-SC(=O)OR^1$, $-NR^1(OR^2)$, $-NR^1R^2$, $-NR^1C(=O)R^2$, $-NR^1C(=O)OR^2$, $-NR^1S(=O)_2R^2$, $-N[S(=O)_2R^1]C(=O)OR^2$, $-S(=O)_2R^1$ and $-S(=O)_2OR^1$;

R^{25} is selected from: OR^5, SR^5 and $-NR^5R^6$, where the group NR^5R^6 is optionally a heterocyclic ring which may contain at least one additional heteroatom selected from: O, S and N;

including racemic, R and S configurations of the compounds, as well as geometrical E/Z or syn/anti isomers, arising from any asymmetric center in the compounds.

In a fourth embodiment of the invention, there are provided novel compounds of the general formula (Id), or prodrugs, tautomeric forms, stereoisomers, pharmaceutically acceptable salts, pharmaceutically acceptable solvates or polymorphs thereof;

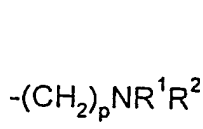


(Id)

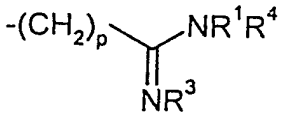
wherein

R^A is selected from: $-NO_2$, -CN, $-C(=O)-NR^1R^2$, $-C(=S)NR^1R^2$, $-C(=NR^1)$-SMe and $-C(=NR^1)$-OMe; or

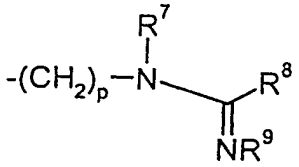
R^A is selected from one of the following groups of formula 2, formula 3 or formula 4;



Formula 2



Formula 3



Formula 4

wherein p is 0, 1 or 2;

R^1 and R^2 , which are independent of each other and can be the same or different, are selected from: H, C_1-C_{13} alkyl, partially or fully fluorinated C_1-C_{10}

alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{17} arylalkyl and C_3-C_{15} heterocycle, or

R^1 and R^2, together with the nitrogen atom to which they are attached, form a saturated, partially saturated, or aromatic heterocycle, which optionally contains at least one additional hetero atom selected from: N, O and S;

R^3 and R^4 , which are independent of each other and can be the same or different, are selected from: H, R^1 or R^2, $-OR^5$, SR^5, $-NR^5R^6$, $-S(=O)_2NR^5R^6$, $-S(=O)_2R^5$, $-C(=O)R^5$, $-C(=O)NR^5R^6$, $-C(=O)OR^5$, $-C(=O)SR^5$, $OC(=O)R^5$, $OC(=O)OR^5$, $OC(=O)NR^5R^6$, $OS(=O)_2R^5$ and $OS(=O)_2NR^5R^6$, wherein R^5 and R^6, which are independent of each other and can be the same or different, are selected from: H, C_1-C_{13} alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{17} arylalkyl and C_3-C_{13} heterocycle and wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkylalkyl group optionally contains at least one hetero atom selected from: N, O and S, anywhere in the chain, including the terminal position, or

R^3 and R^4, together with the respective nitrogen atoms to which they are attached, form a 5-7 membered partially saturated or aromatic heterocycle;

R^7 and R^9 are interchangeable and have the same meaning as R^3 and R^4, defined above;

R^8 is selected from: H, C_1-C_{13} alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{15} arylalkyl and C_3-C_{13} heterocycle, wherein said heterocycle is saturated, partially saturated or aromatic and contains at least one hetero atom selected from: N, O and S; with its point of attachment either through C or N; and wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkylalkyl group optionally contains at least one hetero atom selected from: N, O and S, anywhere in the chain, including the terminal position;

X is selected from: C_1-C_{13} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{15} arylalkyl and C_3-C_{13} heterocycle, or

X is an atom or group selected from: -F, -Cl, -Br, -I, -CN, -NC, $-NO_2$ $-NR^{10}R^{11}$, $-OR^{10}$, $-SR^{10}$, $S(O)R^{10}$, $S(O)_2R^{10}$, $-NHOR^{10}$, $-NHC(=O)R^{10}$, $-NHC(=O)OR^{10}$, $-OC(=O)R^{10}$, $-SC(=O)R^{10}$, $-OC(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, $-C(=O)R^{10}$ and $-C(=O)OR^{10}$, wherein R^{10} and R^{11} have the same meaning as R^5 or R^6, defined above;

Y^1 and Y^2, together, are selected from: =O, =S, $=CR^{12}R^{13}$, $=NR^{12}$ and $=N\text{-}OR^{12}$, wherein R^{12} and R^{13}, which are independent of each other and can be the same or different, are selected from: C_1-C_{11} alkyl, C_2-C_{11} alkenyl, C_2-C_{11} alkynyl, C_3-C_{11} cycloalkyl, C_4-C_{13} cycloalkylalkyl and C_6-C_{13} aryl;

W is selected from: CR^BR^C, O and N, or

W is C_1-C_3 alkylene or C_2-C_3alkenylene, optionally containing at least one hetero atom selected from: O, N and S, wherein at least one ring member of W is optionally substituted by at least one R^B or R^C;

R^B and R^C, which are independent of each other and can be the same or different, are selected from: R^5, = O, $=NR^{14}$, =S, CN, $NR^{14}R^{15}$, OR^{14}, SR^{14}, $S(=O)_2R^{16}$ and COR^{16}, wherein R^{14} and R^{15} have the same meaning as R^5 or R^6, defined above;

R^{16} is selected from: H, OR^{14}, $N(R^{14})_2$, $NR^{14}R^{15}$, SR^{14} and R^5, wherein R^5, R^{14} and R^{15} are as defined above;

n is 0, 1, 2, 3, 4 or 5;

R^D and R^E, which are independent of each other and can be the same or different, are selected from: H, C_1-C_{13} alkyl, partially or fully fluorinated C_1-C_8 alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{13} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{13} aryl, C_7-C_{17} arylalkyl and C_3-C_{13} heterocycle, where the C_1-C_{13} alkyl optionally contains at least one hetero atom selected from: N, O and S , and the C_1-C_{13} alkyl is optionally substituted with at least one functional group selected from: $-OR^{17}$, $-SR^{17}$, $-NR^{17}R^{18}$, $-NHC(=O)R^{17}$, $-NHC(=O)OR^{17}$, $-OC(=O)R^{17}$, $-SC(=O)R^{17}$, $-OS(=O)_2R^{17}$ and $-NHS(=O)_2R^{17}$, wherein R^{17} and R^{18} have the same meaning as R^5 and R^6, defined above; or

when n is 0, optionally one of the groups R^D and R^E is H, and the other is the side chain of an amino acid, the amino acid being either in its natural S configuration, unnatural R configuration or as a racemic mixture;

R^F is selected from: (H, H) (H, OH), O and S;

R^G is selected from: mono or polycyclic aryl, heteroaryl and partially or fully saturated heterocyclic ring, substituted by at least one group selected from: $-R^5$, -F, -Cl, -Br, -I, -CN, SCN, CNO, $-OR^{21}$, $-OC(=O)R^{21}$, $-OS(=O)R^{21}$, $-OS(=O)_2NR^{21}R^{22}$, $-OC(=O)OR^{21}$, $-OC(=O)SR^{21}$, $-OC(=O)\ NR^{21}R^{22}$, $-SR^{21}$, $-S(=O)R^{21}$, $-S(=O)_2R^{21}$, $-NO_2$, $-NR^{21}(OR^{22})$, $-NR^{21}R^{22}$ $-NR^{21}C(=O)R^{22}$, $-N(R^{21})C(=O)OR^{22}$, $-NR^{21}S(=O)_2R^{22}$, $-N[S(=O)_2R^{21}]R^{22}$, $-C(=O)OR^{21}$, $-S(=O)_2R^{22}$, wherein R^{21} and R^{22} have same meaning as R^1 or R^2 as defined above , and a group of the following formula 5;

$$T\text{-}(CH_2)_q\text{-}CR^{23}R^{24}\text{-}COR^{25} \qquad \text{(Formula 5)}$$

wherein

T is selected from: $-CH_2$, O, S and N;

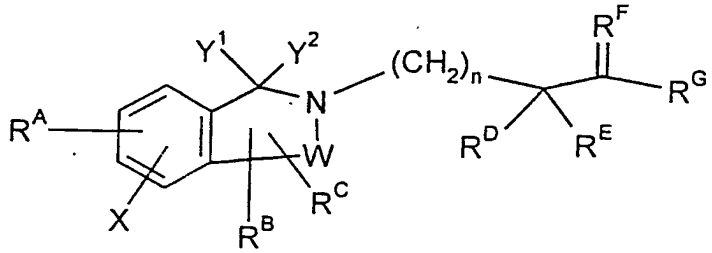
q is 0, 1, 2 or 3;

R^{23} and R^{24} , which are independent of each other and can be the same or different, are selected from: R^5, $C(=O)R^{25}$, $(C_1\text{-}C_{13})$ alkyl and $C_2\text{-}C_{13}$ alkenyl, wherein said alkyl and alkenyl contain at least one hetero atom selected from: O, S, N, in any position , or said alkyl or alkenyl is substituted with at least one group selected from: $-OR^1$, $-OC(=O)R^1$ $-OS(=O)_2R^1$, $-S(=O)_2NR^1R^2$, $-OC(=O)OR^1$, $-OC(=O)SR^1$, $-OC(=O)\ NR^1R^2$, $-SR^1$, $-S(=O)R^1$, $-S(=O)_2R^1$, $-SC(=O)H$, $-SC(=O)OR^1$, $-NR^1(OR^2)$, $-NR^1R^2$, $-NR^1C(=O)R^2$, $-NR^1C(=O)OR^2$, $-NR^1S(=O)_2R^2$, $-N[S(=O)_2R^1]C(=O)OR^2$, $-S(=O)_2R^1$ and $-S(=O)_2OR^1$;

R^{25} is selected from: OR^5, SR^5 and $-NR^5R^6$, wherein the group NR^5R^6 is optionally a heterocyclic ring which may contain at least one additional heteroatom selected from: O, S and N;

including racemic, R and S configurations of the compounds, as well as geometrical E/Z or syn/anti isomers, arising from any asymmetric center in the compounds.

In a fifth embodiment of the invention, there are provided novel compounds of the general formula (Ie), or prodrugs, tautomeric forms, stereoisomers, pharmaceutically acceptable salts, pharmaceutically acceptable solvates or polymorphs thereof:

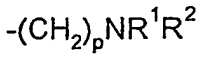


(Ie)

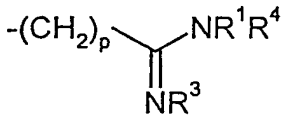
wherein

R^A is selected from: $-NO_2$, -CN, $-C(=O)-NR^1R^2$, $-C(=S)NR^1R^2$, $-C(=NR^1)$-SMe and $-C(=NR^1)$-OMe, or

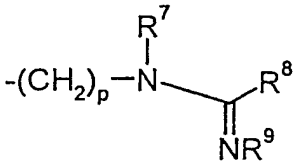
R^A is selected from one of the following groups of formula 2, formula 3 or formula 4;



Formula 2



Formula 3



Formula 4

wherein p is 0, 1 or 2;

R^1 and R^2 , which are independent of each other and can be the same or different, are selected from: H, C_1-C_{13} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{17} arylalkyl and C_3-C_{15} heterocycle; or

R^1 and R^2, together with the nitrogen atom to which they are attached, form a saturated, partially saturated, or aromatic heterocycle which may contain at least one additional hetero atom selected from: N, O and S;

R^3 and R^4 , which are independent of each other and can be the same or different, are selected from: H, R^1, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-S(=O)_2NR^5R^6$, $-S(=O)_2R^5$, $-C(=O)R^5$, $-C(=O)NR^5R^6$, $-C(=O)OR^5$, $-C(=O)SR^5$, $OC(=O)R^5$, $OC(=O)OR^5$, $OC(=O)NR^5R^6$, $OS(=O)_2R^5$ and $OS(=O)_2NR^5R^6$; wherein R^5 and R^6 , which are independent of each other and can be the same or different, are selected from: H, C_1-C_{13} alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl,

C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{17} arylalkyl and C_3-C_{13} heterocycle, and said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkylalkyl optionally contain at least one hetero atom selected from: N, O and S, anywhere in the chain, including the terminal position, or

R^3 and R^4, together with the respective nitrogen atoms to which they are attached, optionally form a 5-7 membered partially saturated or aromatic heterocycle;

R^7 and R^9 are interchangeable and have the same meaning as R^3 and R^4, defined above;

R^8 is selected from: H, C_1-C_{13} alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{15} arylalkyl and C_3-C_{13} heterocycle, wherein said heterocycle is saturated, partially saturated or aromatic and contains at least one hetero atom selected from: N, O and S, with its point of attachment either through C or N; and wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkylalkyl groups optionally contain at least one hetero atom selected from: N, O and S, anywhere in the chain, including the terminal position;

X is selected from: C_1-C_{13} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{15} arylalkyl and C_3-C_{13} heterocycle, or

X is an atom or group selected from: -F, -Cl, -Br, -I, -CN, -NC, $-NO_2$, $-NR^{10}R^{11}$, $-OR^{10}$, $-SR^{10}$, $S(O)R^{10}$, $S(O)_2R^{10}$, $-NHOR^{10}$, $-NHC(=O)R^{10}$, $-NHC(=O)OR^{10}$, $-OC(=O)R^{10}$, $-SC(=O)R^{10}$, $-OC(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, $-C(=O)R^{10}$ and $-C(=O)OR^{10}$, wherein R^{10} and R^{11} have the same meaning as R^5 or R^6, defined above;

Y^1 and Y^2, together, are selected from: =O, =S and $=CR^{12}R^{13}$, wherein R^{12} and R^{13} have the same meaning as R^5 and R^6, defined above;

W is selected from: $-CH_2-$, $-CH_2-CH_2-$, -CH=CH- , -C-N-, -C=N-, -C-O-, -C-S- , -O- , -NH- and -N=N-, which groups are optionally substituted by at least one of R^B and R^C;

R^B and R^C , which are independent of each other and can be the same or different, are selected from: R^5, = O, $=NR^{14}$, =S, CN, $NR^{14}R^{15}$, OR^{14}, SR^{14}, $S(=O)_2R^{16}$ and COR^{16}, wherein $R^{14}$and R^{15} have the same meaning as R^5 or R^6, defined above ;

R^{16} is selected from: H, OR^{14}, $N(R^{14})_2$, $NR^{14}R^{15}$, SR^{14} and R^5, as defined above;

n is 0, 1, 2, 3, 4 or 5;

R^D and R^E , which are independent of each other and can be the same or different, are selected from: H, C_1-C_{13} alkyl, C_1-C_8 partially or fully fluorinated alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{13} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{13} aryl, C_7-C_{17} arylalkyl and C_3-C_{13} heterocycle, where the C_1-C_{13} alkyl optionally contains at least one hetero atom selected from: N, O and S, and the C_1-C_{13} alkyl is optionally substituted with at least one functional group selected from, for example: $-OR^{17}$, $-SR^{17}$, $-NR^{17}R^{18}$, $-NHC(=O)R^{17}$, $-NHC(=O)OR^{17}$, $-OC(=O)R^{17}$, $-SC(=O)R^{17}$, $-OS(=O)_2R^{17}$ and $-NHS(=O)_2R^{17}$, wherein R^{17} and R^{18} have the same meaning as R^5 and R^6, defined above, or

when n is 0, optionally one of the groups R^D and R^E is H, and the other is the side chain of an amino acid, the amino acid being either in its natural S configuration, unnatural R configuration or as a racemic mixture;

R^F is selected from: (H, H), O and S;

R^G is selected from: a mono- or polycyclic aryl, heteroaryl and partially or fully saturated heterocyclic ring, substituted by at least one group selected from: $-R^5$, -F, -Cl, -Br, -I, -CN, -SCN, -CNO, $-OR^{21}$, $-OC(=O)R^{21}$, $-OS(=O)_2R^{21}$, $-OS(=O)_2NR^{21}R^{22}$, $-OC(=O)OR^{21}$, $-OC(=O)SR^{21}$, $-OC(=O)\ NR^{21}R^{22}$, $-SR^{21}$, $-S(=O)R^{21}$, $-S(=O)_2R^{21}$, $-NO_2$, $-NR^{21}(OR^{22})$, $-NR^{21}R^{22}$ $-NR^{21}C(=O)R^{22}$, $-N(R^{21})C(=O)OR^{22}$, $-NR^{21}S(=O)_2R^{22}$, $-N[S(=O)_2R^{21}]R^{22}$, $-C(=O)OR^{21}$ and $-S(=O)_2R^{21}$, wherein R^{21} and R^{22} have the same meaning as R^1 and R^2 as defined above, and a group of the following formula 5;

$$T\text{-}(CH_2)_q\text{-}CR^{23}R^{24}\text{-}COR^{25} \qquad \text{(Formula 5)}$$

wherein

T is selected from: $-CH_2$, O, S and N;

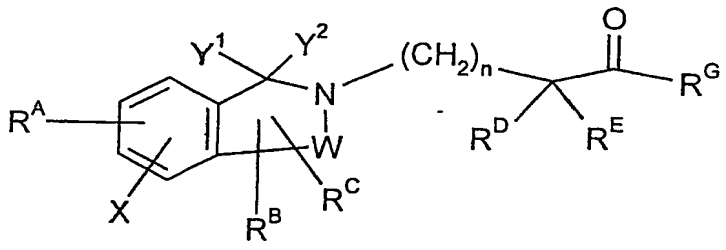
q is 0, 1, 2 or 3;

R^{23} and R^{24}, which are independent of each other and can be the same or different, are selected from: R^5, $C(=O)R^{25}$, $(C_1\text{-}C_{13})$ alkyl and $(C_2\text{-}C_{13})$ alkenyl, wherein said alkyl and alkenyl contain at least one hetero atom selected from: O, S and N or said alkyl and alkenyl are substituted with at least one group selected from: $-OR^1$, $-OC(=O)R^1$ $-OS(=O)_2R^1$, $-S(=O)_2NR^1R^2$, $-OC(=O)OR^1$, $-OC(=O)SR^1$, $-OC(=O)\ NR^1R^2$, $-SR^1$, $-S(=O)R^1$, $-S(=O)_2R^1$, -SC(=O)H, $-SC(=O)OR^1$, $-NR^1(OR^2)$, $-NR^1R^2$, $-NR^1C(=O)R^2$, $-NR^1C(=O)OR^2$, $-NR^1S(=O)_2R^2$, $-N[S(=O)_2R^1]C(=O)OR^2$, $-S(=O)_2R^1$ and $-S(=O)_2OR^1$;

R^{25} is selected from: OR^5, SR^5 and $-NR^5R^6$, where the group NR^5R^6 is optionally a heterocyclic ring which may contain at least one additional heteroatom selected from: O, S and N;

including racemic, R and S configurations of the compounds, as well as geometrical E/Z or syn/anti isomers, arising from any asymmetric center in the compounds.

In a sixth embodiment of the invention, there are provided novel compounds of the general formula (If), or prodrugs, tautomeric forms, stereoisomers, pharmaceutically acceptable salts, pharmaceutically acceptable solvates or polymorphs thereof;

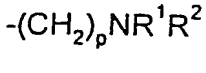


(If)

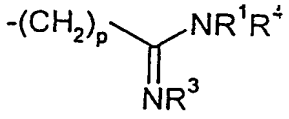
wherein

R^A is selected from: $-NO_2$, -CN, $-C(=O)-NR^1R^2$, $-C(=S)NR^1R^2$, $-C(=NR^1)$-SMe and $-C(=NR^1)$-OMe, or

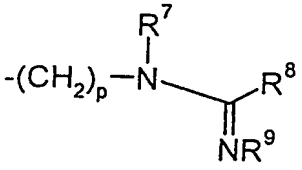
R^A is selected from one of the following groups of formula 2, formula 3 or formula 4;



Formula 2



Formula 3



Formula 4

wherein

p is 0, 1 or 2;

R^1 and R^2 , which are independent of each other and can be the same or different, are selected from: H, C_1-C_{13} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{17} arylalkyl and C_3-C_{15} heterocycle; or

R^1 and R^2, together with the nitrogen atom to which they are attached, form a saturated, partially saturated, or aromatic heterocycle, which may contain at least one additional hetero atom selected from: N, O and S;

R^3 and R^4 , which are independent of each other and can be the same or different, are selected from: H, R^1, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-S(=O)_2NR^5R^6$, $-S(=O)_2R^5$, $-C(=O)R^5$, $-C(=O)NR^5R^6$, $-C(=O)OR^5$, $-C(=O)SR^5$, $OC(=O)R^5$, $OC(=O)OR^5$, $OC(=O)NR^5R^6$, $OS(=O)_2R^5$ and $OS(=O)_2NR^5R^6$, wherein R^5 and R^6 , which are independent of each other and can be the same or different, are selected from: H, C_1-C_{13} alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{17} arylalkyl and C_3-C_{13} heterocycle, wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkylalkyl optionally contain at least one hetero atom selected from: N, S and O, anywhere in the chain, including the terminal position, or

R^3 and R^4, together with the respective nitrogen atoms to which they are attached, form a 5-7 membered partially saturated or aromatic heterocycle;

R^7 and R^9 are interchangeable have the same meaning as R^3 and R^4, defined above;

R^8 is selected from: H, C_1-C_{13} alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{15} arylalkyl and C_3-C_{13}

heterocycle, wherein said heterocycle is saturated, partially saturated or aromatic and contains at least one hetero atom selected from: N, O and S, with its point of attachment either through C or N; and wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkylalkyl optionally contain at least one hetero atom selected from: N, O and S, anywhere in the chain, including the terminal position;

X is selected from: C_1-C_{13} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{12} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{15} aryl, C_7-C_{15} arylalkyl and C_3-C_{13} heterocycle, or

X is an atom or group selected from, for example: -F, -Cl, -Br, -I, -CN, -NC, -NO_2, -$NR^{10}R^{11}$, -OR^{10}, -SR^{10}, $S(O)R^{10}$, $S(O)_2R^{10}$, -$NHC(=O)R^{10}$, -$NHOR^{10}$, -$OC(=O)R^{10}$, -$SC(=O)R^{10}$, -$NHC(=O)OR^{10}$, -$OC(=O)OR^{10}$, -$C(=O)NR^{10}R^{11}$, -$C(=O)R^{10}$ and -$C(=O)OR^{10}$, wherein R^{10} and R^{11} have the same meaning as R^5 or R^6, defined above;

Y^1 and Y^2, together, are selected from: =O and =S;

W is selected from: -CH_2-, -CH_2 CH_2-, -CH=CH-, -C-N-, -C=N-, -C-O-, -C-S- -O-, -NH- and -N=N-, each of which are optionally substituted by at least one of the groups R^B and R^C;

R^B and R^C, which are independent of each other and can be the same or different, are selected from: R^5, = O, =NR^{14}, =S, CN, $NR^{14}R^{15}$, OR^{14}, SR^{14}, $S(=O)_2N^{16}$ and COR^{16}, wherein R^{14} and R^{15} have the same meaning as R^5 or R^6, defined above,
R^{16} is selected from: H, OR^{14}, $N(R^{14})_2$, $NR^{14}R^{15}$, SR^{14} and R^5, defined above;

n is 0, 1, 2 or 3;

R^D and R^E , which are independent of each other and can be the same or different, are selected from: H, C_1-C_{13} alkyl, partially or fully fluorinated C_1-C_8 alkyl, C_2-C_{13} alkenyl, C_2-C_{13} alkynyl, C_3-C_{13} cycloalkyl, C_4-C_{15} cycloalkylalkyl, C_6-C_{13} aryl, C_7-C_{17} arylalkyl and C_3-C_{13} heterocycle, where the C_1-C_{13} alkyl optionally contains at least one hetero atom selected from: O, S and N and the C_1-C_{13} alkyl optionally contains at least one functional group selected from: -OR^{17}, -SR^{17}, -$NR^{17}R^{18}$, -$NHC(=O)R^{17}$, -$NHC(=O)OR^{17}$, -$OC(=O)R^{17}$, -$SC(=O)R^{17}$, -$OS(=O)_2R^{17}$ and -$NHS(=O)_2R^{17}$, wherein R^{17} and R^{18} have the same meaning as R^5 and R^6, defined above, or

when n is 0, optionally one of the groups R^D and R^E is H, and the other is the side chain of an amino acid, the amino acid being either in its natural S configuration, unnatural R configuration or as a racemic mixture;

R^G is selected from: mono- or polycyclic aryl, heteroaryl and partially or fully saturated heterocyclic, substituted by at least one group of formula 5 and, optionally, further substituted by at least one group selected from: –R^5, -F, -Cl, -Br, -I, -CN, -SCN, -CNO, -OR^{21}, -$OC(=O)R^{21}$, -$OS(=O)_2R^{21}$, -$OS(=O)_2NR^{21}R^{22}$, -$OC(=O)OR^{21}$, -$OC(=O)SR^{21}$, -$OC(=O)$ $NR^{21}R^{22}$, -SR^{21}, -$S(=O)R^{21}$, -$S(=O)_2R^{21}$, -NO_2, -$NR^{21}(OR^{22})$, -$NR^{21}R^{22}$ –$NR^{21}C(=O)R^{22}$, -$N(R^{21})C(=O)OR^{22}$, -$NR^{21}S(=O)_2R^{22}$, -$N[S(=O)_2R^{21}]R^{22}$, -$C(=O)OR^{21}$ and -$S(=O)_2R^{21}$, wherein R^{21} and R^{22} have same meaning as R^1 or R^2 , defined above, and the group of formula 5 is:

$$T\text{-}(CH_2)_q\text{-}CR^{23}R^{24}\text{-}COR^{25} \qquad \text{(Formula 5)}$$

wherein

T is selected from: -CH_2, O, S and N;

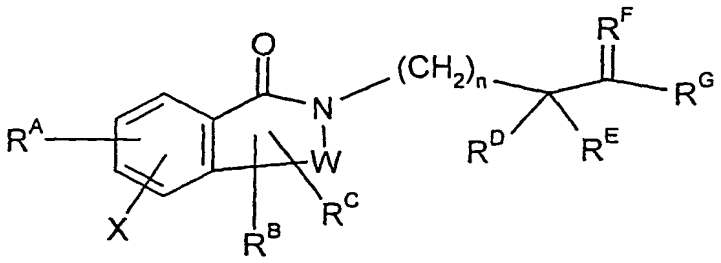
q is 0, 1, 2 or 3;

R^{23} and R^{24}, which are independent of each other and can be the same or different, are selected from: R^5, $C(=O)R^{25}$, C_1-C_{13} alkyl and C_2-C_{13} alkenyl, such that said alkyl and alkenyl have at least one hetero atom selected from: O, S and N or said alkyl and alkenyl are substituted with at least one group selected from: $-OR^1$, $-OC(=O)R^1$, $-OS(=O)_2R^1$, $-S(=O)_2NR^1R^2$, $-OC(=O)OR^1$, $-OC(=O)SR^1$, $-OC(=O)NR^1R^2$, $-SR^1$, $-S(=O)R^1$, $-S(=O)_2R^1$, $-SC(=O)H$, $-SC(=O)OR^1$, $-NR^1(OR^2)$, $-NR^1R^2$, $-NR^1C(=O)R^2$, $-NR^1C(=O)OR^2$, $-NR^1S(=O)_2R^2$, $-N[S(=O)_2R^1]C(=O)OR^2$, $-S(=O)_2R^1$ and $-S(=O)_2OR^1$;

R^{25} is selected from: OR^5, SR^5 and $-NR^5R^6$, where NR^5R^6 optionally forms a heterocyclic ring which may contain an additional heteroatom selected from: O, S and N;

including racemic, R and S configurations of the compounds, as well as geometrical E/Z or syn/anti isomers, arising from any asymmetric center in the compounds.

In a seventh embodiment of the invention there are provided novel compounds of the general formula (Ig), or prodrugs, tautomeric forms, stereoisomers, pharmaceutically acceptable salts, pharmaceutically acceptable solvates or polymorphs thereof:



(Ig)

wherein

R^A, R^B, R^C, R^D, R^E, R^F and n are as defined above in respect of general formula (I) or general formulae (Ia) to (If);

X is as defined above in respect of general formula (Ic) to (If);

R^G is selected from: phenyl, piperidinyl and piperazinyl, substituted with

(a) at least one substituent selected from: $T(CH_2)_qCR^{23}R^{24}COR^{25}$ (formula 5), OCH_2Phenyl and $-CH_2C(O)\ R^{25}$, wherein T, R^{23}, R^{24}, R^{25} and q are as defined above in respect of geneal formula (I) or general formulae (Ia) to (If), and

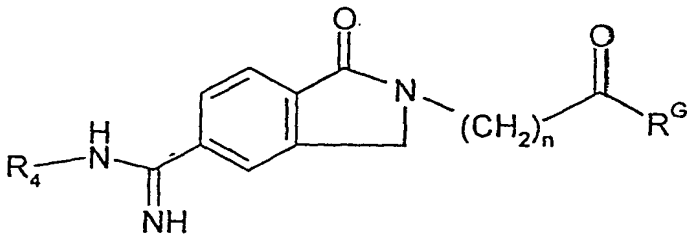
(b) optionally at least one further substituent selected from: $-R^5$, -F, -Cl, -Br, -I, -CN, -SCN, -CNO, $-OR^{21}$, $-OC(=O)R^{21}$, $-OS(=O)_2R^{21}$, $-OS(=O)_2NR^{21}R^{22}$, $-OC(=O)OR^{21}$, $-OC(=O)SR^{21}$, $-OC(=O)\ NR^{21}R^{22}$, $-SR^{21}$, $-S(=O)R^{21}$, $-S(=O)_2R^{21}$, -SC(=O)H, $-SC(=O)OR^{21}$, $-NO_2$, $-NR^{21}(OR^{22})$, $-NR^{21}R^{22}$, $-NR^{21}C(=O)R^{22}$, $-N(R^{21})C(=O)OR^{22}$, $-NR^{21}S(=O)_2R^{22}$, $-N[S(=O)_2R^{21}]\ R^{22}$, $C(=O)OR^{21}$, $-S(=O)_2R^{21}$ and $-S(=O)_2OR^{21}$, wherein R^{21} and R^{22} , which are independent of each other and can be the same or different, are selected from: H, C_1-C_{15} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{15} alkenyl, C_2-C_{15} alkynyl, C_3-C_{15} cycloalkyl, C_4-C_{15} cycloalkylalkyl, monocyclic or polycyclic aryl, C_7-C_{17} arylalkyl and C_3-C_{15} heterocycle; or, in the case of the substituents: $OC(=O)\ NR^{21}R^{22}$ and $-NR^{21}R^{22}$, R^{21} and R^{22}, together with the nitrogen atom to which they are attached, form a saturated, partially saturated or aromatic heterocycle, which optionally contains at least one additional hetero atom selected from: N, O and S; and

W is CH_2 or $CH_2\ CH_2$;

including racemic, R and S configurations of the compounds, as well as geometrical E/Z or syn/anti isomers, arising from any asymmetric center in the compounds.

The amino acid referred to in the definition of R^D and R^E in respect of general formula (I) or general formula (Ia) to (Ig) may be selected from L-Tyrosine, Glycine, or β-Alanine etc.

In an eighth embodiment of the invention there are provided novel compounds of the general formula (Ih), or prodrugs, tautomeric forms, stereoisomers, pharmaceutically acceptable salts, pharmaceutically acceptable solvates or polymorphs thereof:



(Ih)

wherein

R^G is phenyl, piperidinyl or piperazinyl, substituted with:

(a) at least one substituent selected from: $-CH_2C(O)R^{25}$ and $-T-(CH_2)q-CH_2-C(O)R^{25}$, wherein T is CH_2, O, S or NH, q is 0, 1, 2 or 3, R^{25} is selected from: OR^5 and NR^5R^6, wherein R^5 and R^6, which are independent of each other and can be the same or different, are selected from: H, C_1-C_6-alkyl and phenyl; and, optionally,

(b) at least one substituent selected from: -OH, $-NH-C(O)CH_3$ and C_1-C_6-alkyl;

R_4 is selected from: H, OH, -C(O)OH and $-C(O)OC_1$-C_6-alkyl;
n is 1 or 2;

including racemic, R and S configurations of the compounds, as well as geometrical E/Z or syn/anti isomers, arising from any asymmetric center in the compounds.

As described in more detail below, the present invention further relates to processes for the preparation of compounds of general formula (I) or general formulae (Ia) to (Ih), to their use as active ingredients in pharmaceuticals, alone or in combination with other therapeutic agents, in particular for the inhibition of platelet aggregation and for the treatment of thrombotic disorders in mammals, especially humans.

Listed below are definitions of various terms used to describe the compounds of the present invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or as part of a larger group. They should not be interpreted in the literal sense. They are not general definitions and are relevant only for this application.

The term "heterocycle" or "heterocyclic" can be defined as a stable 3-7 membered monocyclic or bicyclic, for example 7-10 membered bicyclic, ring which may be saturated, partially saturated or aromatic in nature. Besides carbon atoms, the ring contains 1-4 heteroatoms. The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen (N), oxygen (O), sulfur (S) and phosphorous (P). The atoms N and S can exist in oxidized form and N can be quaternized. The terms "heterocycle" and "heterocyclic" include a bicyclic ring comprising a heterocyclic ring as defined above fused to a benzene ring. The attachment of above

defined heterocyclic ring to the main structure may be through a carbon atom or a heteroatom provided that a stable structure results.

The above defined heterocyclic ring may be substituted anywhere in the ring provided that a stable structure is obtained. Examples of such heterocycles include, but are not limited to, acridinyl, azocinyl, benzofuranyl, benzimidazolyl, benzothiophenyl, carbazolyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, furanyl (furyl), furazanyl, imidazolyl, imidazolinyl, indolenyl, indolizinyl, indolyl, indolinyl, 1H-indazolyl, isobenzofuranyl, isoindolinyl, isooxazolyl, isooxazolinyl, isoquinolinyl, isothiazolyl, morpholinyl, octahydroisoquinolinyl, oxazolidinyl, phenoxathinyl, phenazinyl, piperidinyl, piperazinyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazolinyl, pyrazolyl, pyrazolidinyl, pyrazinyl, pyridyl (pyridinyl), pyrimidinyl, pyridazinyl, pyrrolyl, pyrrolidinyl, pyrrolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinazolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, thiazolyl, triazinyl, thienyl, 6H-1,2,5-thiadiazinyl and xanthenyl.

It should be noted that any heteroatom with unsatisfied valences is assumed to have the hydrogen atom to satisfy the valences.

Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine.

As used herein, the term "alkyl" includes both branched and straight chain saturated aliphatic hydrocarbons having a specified number of carbon atom(s); examples of such groups include, but are not limited to, methyl, ethyl, propyl, butyl, isopentyl, neopentyl, and hexyl; the term "cycloalkyl" is intended to include a saturated mono-, bi- or poly- cyclic ring system containing a specified number of carbon atom(s); examples of such groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclohexyl, adamantyl, [3,3,0]bicyclooctanyl and [4.4,0]bicyclodecanyl; the term "cycloalkylalkyl" is intended to include connection

of a cycloalkyl group defined above via an alkyl group in which total number of carbon atoms cannot exceed the specified requisite number; examples of such groups include, but are not limited to, 2-cyclopropylethyl and 3-cyclohexyl-2-methylpropyl.

Unless stated otherwise, and irrespective of any specific substituents bonded to alkyl groups that are indicated in the definition of the compounds of the general formula (I) or general formulae (Ia) to (Ih), alkyl groups can in general be unsubstituted or substituted by at least one, for example 1, 2, 3, 4 or 5, identical or different substituents. Any kind of substituents present in substituted alkyl residues can be present in any desired position provided that the substitution does not lead to an unstable molecule. A substituted alkyl refers to an alkyl residue in which at least one, for example, 1, 2, 3, 4 or 5, hydrogen atoms are replaced with substituents, for example, halogen, hydroxyl, carbonyl, alkoxyl, ester, ether, cyano, amino, amido, imino, sulfhydryl, alkylthio, thioester, sulfonyl, nitro, heterocyclic, aralkyl, or an aryl or heteroaryl group. The carbon backbone of the alkyl group may be interrupted by heteroatoms such as oxygen, sulphur or nitrogen. Examples of substituted acyclic alkyls are: hydroxymethyl, hydroxyethyl, 2-hydroxyethyl, aminoethyl or morpholinoethyl. Examples of substituted cycloalkyl groups are: cycloalkyl groups which carry as substituent at least one , for example 1, 2, 3, 4 or 5, identical or different acyclic alkyl groups, for example acyclic (C_1-C_4)-alkyl groups like methyl groups. Examples of substituted cycloalkyl groups are 4-methylcyclohexyl, 4-tert-butylcyclohexyl and 2,3-dimethylcyclopentyl.

It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can them selves be substituted, if appropriate. For example, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, imino, amido, sulfonyl (including sulfonate and sulfonamide), as well as ether, alkylthio, carbonyl (including ketones, aldehydes, carboxylates, and esters), $-CF_3$, -CN and the like. Cycloalkyls can be further substituted with alkyl,

alkenyl, alkoxyl, alkylthio, aminoalkyls, carbonyl-substituted alkyl, $-CF_3$, cyano (CN), and the like.

The term "alkenyl" as used herein can be defined as a straight or branched hydrocarbon chain having a specific number of carbon atoms containing one or more carbon-carbon double bonds present anywhere in the carbon chain provided that a stable compound is formed; examples of such a group include, but are not limited to: ethenyl, propenyl and pent-2-enyl.

As used herein the term "alkynyl" is defined as a straight or branched chain hydrocarbon chain having a specified number of carbon atoms which contain one or more carbon-carbon triple bonds present anywhere in the chain provided that a stable compound results; examples of such a group include, but are not limited to: ethynyl and propynyl.

The terms "alkylene", "alkenylene" and "phenylene" are intended to refer to alkyl, alkenyl and phenyl groups, respectively, which are connected by two bonds to the rest of the structure as indicated in the structure of general formula (I) or the structures of general formulae (Ia) to (Ih) or substructures or partial structures thereof, wherever applicable.

The term "aryl" as used herein refers to monocyclic or polycyclic hydrocarbon groups having up to 14 ring carbon atoms in which at least one carbocyclic ring is present that has a conjugated pi electron system. Examples of (C_6-C_{20})-aryl residues are phenyl, naphthyl, biphenyl, fluorenyl and anthracenyl. The term "arylalkyl" indicates an aryl group as defined above which is attached to the indicated position through an alkyl bridge.

As used herein the terms "substituted", "substitution" or substituent" have the meaning that one or more hydrogens on the specified atom are replaced with an atom or group selected from a defined atom or group, such that the normal

valence of the atom involved is not exceeded and a stable compound is provided. When a bond to a substituent is shown drawn across the bond connecting any two given atoms in a ring, then such substituent may be connected to any atom in the ring; an example of such a group, without intending to be limiting, is R^A in the general formula (I) or general formulae (Ia) to (Ig) which may be connected to any ring member of ring A ; similarly when a bond between an atom or group to another atom or group is not specifically shown, such bond may be formed with any atom or group and other such atom or group. When a substituent is listed without mention of its mode of connection i.e., the atom through which the bond is formed, then such substituent is considered to be connected via any atom in such substituent; for example a substituent shown as -O-CH=CH- includes both the substituents –O-CH=CH- and -CH=CH-O-.

When an undefined multiple bond is drawn between an atom or group and another atom or group symbolised by an alphabet, such a multiple bond is intended to mean a double or triple bond as well as two or three single bonds, respectively, at the designated point of attachment. An example of such a connection is $C=R^F$ in general formula (I), which can be defined as C=O, CH(OH) or CH_2 and the like.

A combination of substituent(s) and/or variable(s) leading to stable compound is permissible in the present invention.

As used herein a stable compound can be defined as one which can sustain the steps involved in its isolation from the reaction mixture to a useful degree of purity and subsequent formulation into an efficacious therapeutic agent.

"Activation" refers to the change in conformation and the subsequent exposure of the otherwise inactive and unexposed GP IIb/IIIa receptors.

"Platelet aggregation" refers to the formation of clumps of platelets, which occur when fibrinogen molecules bind to the activated GP IIb/IIIa receptors and cross-link platelets.

"Thrombi" are clusters of cross-linked platelets, sometimes containing trapped red blood cells.

"GP IIb/IIIa receptors" are glycoprotein receptors on the surface of platelets, which when activated recognize the Arginine-Glycine-Aspartic acid (RGD) sequence in the fibrinogen molecules.

"Thrombocytopenia" is defined as a reduction in the number of circulating free platelets.

It is also to be understood that compounds of the present invention may have asymmetric centers; all enantiomers, diastereomers and racemic forms are included within the scope of the present invention. It is further understood that geometric isomers of olefins, C=N and conformational isomers or isomers arising out of restricted rotation, as well understood by those familiar to the art of organic chemistry, are also included within the scope of the present invention. The present invention also includes all possible enantiomers and diastereomers in pure or substantially pure form and mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or diastereomers, in all ratios.

Prodrugs are considered to be any covalently bonded carriers that release the active parent drug in vivo. In other words, a prodrug when absorbed in the blood stream cleaves in such a manner as to release the drug molecule to generate desired therapeutic efficacy. Prodrugs include compounds of general formula (I) or (Ia) to (Ih) wherein hydroxyl, amino, amidino, sulfhydryl or carboxylic groups are bonded to any group, which cleaves to form a free hydroxyl, amino, sulfhydryl or carboxyl group, respectively, on administration to a mammalian subject. Thus,

the present invention also includes those compounds produced in vivo after administration of a different compound (or prodrug of the compound). The in vivo effects of compounds described herein, may not be exerted by those compounds as such, but by one or more degradation products.

Compounds of general formula (I) or general formulae (Ia) to (Ih) which contain one or more basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention in the form of their addition salts with non-toxic inorganic or organic acids. Examples of suitable inorganic acids include: boric acid, perchloric acid, hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, phosphoric acid, nitric acid and other inorganic acids known to the person skilled in the art. Examples of suitable organic acids include: acetic acid, propionic acid, succinic acid, glycolic acid, stearic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, pamoic acid, maleic acid, hydroxymaleic acid, phenylacetic acid, glutamic acid, benzoic acid, salicylic acid, sulfanilic acid, 2-acetoxybenzoic acid, fumaric acid, toluenesulfonic acid, methanesulfonic acid, ethane disulfonic acid, oxalic acid, isethionic acid, ketoglutaric acid, benzenesulfonic acid, glycerophosphoric acid and other organic acids known to the person skilled in the art.

The compounds of general formula (I) or general formulae (Ia) to (Ih) which contain acidic groups can be used according to the invention, for example, as alkali metal salts like Li, Na, and K salts, as alkaline earth metal salts like Ca, Mg salts, as aluminium salts, as salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline, tromethamine, or as salts with ammonia.

The pharmaceutically acceptable salts of the present invention can be synthesized from the subject compound which contains a basic or acidic moiety by conventional chemical methods. Generally the salts are prepared by contacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or

dispersant or by anion exchange or cation exchange with other salts. Suitable solvents are, for example, ethyl acetate, ether, alcohols, acetone, THF, dioxane or mixtures of these solvents.

The present invention furthermore includes all solvates of compounds of general formula (I) or general formulae (Ia) to (Ih), for example hydrates or adducts with alcohols.

Various polymorphs of compounds of general formula (I) or general formulae (Ia) to (Ih) forming part of this invention may be prepared by crystallization of compounds of general formula (I) or general formulae (Ia) to (Ih) under different conditions. For example, using different commonly used solvents or their mixtures for crystallization; crystallization at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by IR spectroscopy, solid probe NMR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

Specifically preferred compounds of this invention are compounds that belong to the examples cited below or pharmaceutically acceptable salts thereof selected from but not limited to:

(4- {2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid methyl ester;

(4-{2-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid methyl ester;

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;

(4-{2-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;

4-(2-{5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl}-acetyl]-phenoxy)-acetic

acid isopropyl ester;
(4-{2-[5-(Imino-methoxycarbonylamino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid isopropyl ester;
(4-{2-[5-(Imino-isobutoxycarbonylamino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid isopropyl ester;
(4-{2-[5-(Benzyloxycarbonylamino-imino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid isopropyl ester;
(4-{2-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid isopropyl ester;
(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid isobutyl ester;
(4-{2-[5-(Imino-methoxycarbonylamino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid isobutyl ester;
(4-{2-[5-(Imino-isobutoxycarbonylamino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid isobutyl ester;
(4-{2-[5-(Benzyloxycarbonylamino-imino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid isobutyl ester;
(4-{2-[5-(Imino-methanesulfonylamino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid isobutyl ester;
(4-{2-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy) -acetic acid isobutyl ester;
(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid benzyl ester;
(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid;
(4-{2-[5-(Imino-methoxycarbonylamino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid benzyl ester;
(4-{2-[5-(Imino-isobutoxycarbonylamino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid benzyl ester;
(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-ethoxy carbonyl methoxy-phenoxy)-acetic acid ethyl ester;

(2-Ethoxycarbonylmethoxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}–phenoxy)-acetic acid ethyl ester;

(2-Ethoxycarbonylmethoxy-4-{2-[5-(imino-{3-methyl-butyrylamino}-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}–phenoxy)-acetic acid ethyl ester;

(2-Ethoxycarbonylmethoxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-1-hydroxyimino-ethyl}–phenoxy)-acetic acid ethyl ester;

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}–2-isobutoxy carbonyl methoxy-phenoxy)-acetic acid isobutyl ester;

2-(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-NN-diethyl-acetamide;

4-(2-{4-[2-(5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl)-acetyl]-phenoxy}-acetoxy)-piperidine-1-carboxylic acid benzyl ester;

4-Benzyloxycarbonylamino-2-(4-{2-[5-carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-butyric acid ethyl ester;

4-Benzyloxycarbonylamino-2-(4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-butyric acid ethyl ester;

(4-{2-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenylsulfanyl)-acetic acid methyl ester;

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-chloro-phenoxy)-acetic acid ethyl ester;

(2-Chloro-4-{2-[5-(imino-isobutoxycarbonylamino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;

(2-Chloro-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-ethyl sulfanyl-phenoxy)-acetic acid ethyl ester;

(2-Ethylsulfanyl-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-ethane sulfonyl-phenoxy)-acetic acid ethyl ester;

(2-Ethanesulfonyl-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-

2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;
(2,6-Bis-ethylsulfanyl-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;
(2-Acetylamino-4-{2-[5-N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;
(2-(Ethoxycarbonylmethyl-methanesulfonyl-amino)-4-{2-[5-(imino-isobutoxy carbonylamino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;
(2-(Ethoxycarbonylmethyl-methanesulfonyl-amino)-4-{2-[5-(N-hydroxy carbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;
(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-phenoxy)-acetic acid ethyl ester;
(3-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;
(3-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid benzyl ester;
(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-phenoxy)-acetic acid;
(4-{2-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-methoxy-phenoxy)-acetic acid ethyl ester;
(4-{2-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-propoxy-phenoxy)-acetic acid ethyl ester;
(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-ethoxy carbonylmethoxy-phenoxy)-acetic acid ethyl ester;
(3-Ethoxycarbonylmethoxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid;
(2-Ethylsulfanyl-3-hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;
(2-Ethyl-5-hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;

(5-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-isopropyl-phenoxy)-acetic acid ethyl ester;
(2-*tert*-Butyl-5-hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;
(2-Chloro-5-hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;
(2-Chloro-3-hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;
(3-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-methyl-phenoxy)-acetic acid ethyl ester;
(3-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-methyl-phenoxy)-acetic acid benzyl ester;
(2-Ethyl-3-hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;
(3-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-propyl-phenoxy)-acetic acid ethyl ester;
(3-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-propyl-phenoxy)-acetic acid benzyl ester;
(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-2-propyl-phenoxy)-acetic acid;
(4-Hydroxy-3-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;
(3-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-5-methoxy-phenoxy)-acetic acid ethyl ester;
(3,5-Dihydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;
(2-Ethoxycarbonylmethoxy-3-hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-aceic acid ethyl ester;
(2-Ethoxycarbonylmethoxy-5-hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;
(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-piperazine-1-yl)-

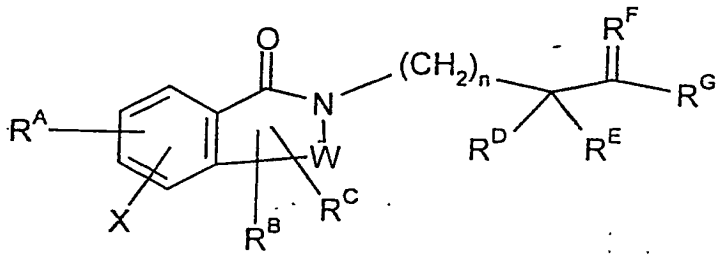
acetic acid ethyl ester;
(1-{2S-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-3-(4-hydroxy-phenyl)-propionyl}-piperidin-4-yloxy)-acetic acid ethyl ester;
(1-{2-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-piperidin-4-yloxy)-acetic acid ethyl ester;
(1-{3-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-propionyl}-piperidin-4-yloxy)-acetic acid ethyl ester;
(1-{2-[5-(5-Methyl-isoxazol-3-yl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-piperidin-4-yloxy)-acetic acid ethyl ester;
(1-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-piperidin-4-yloxy)-acetic acid ethyl ester;
(1-{2-[5-(*tert*-Butoxycarbonylamino-imino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-piperidin-4-yloxy)-acetic acid ethyl ester;
(1-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-piperidin-4-yloxy)-acetic acid;
(4-{2-[5-Acetimidoylamino-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-phenoxy)-acetic acid ethyl ester;
(3-Ethoxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;
(4-[2-(5-carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl)-acetyl]-3-ethoxy-phenoxy}-acetic acid ethyl ester;
(4-{2-[5-Carbamimdoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-ethoxy-phenoxy)-acetic acid;
(3-Hydroxy-4-{2-[1-oxo-5-(5-oxo-2,5-dihydro-[1,2,4]oxadiazol-3-yl)-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;
(4-{2-[5-(Acetylamino-imino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-phenoxy)-acetic acid ethyl ester;
(3-Acetoxy-4-{2-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;
(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-2-propyl-phenoxy)-acetic acid ethyl ester;

(3-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-propyl-phenoxy)-acetic acid;
(3-Allyloxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester;

including the pharmaceutically acceptable salts and solvates of the above listed compounds.

According to a further aspect of the invention, there are provided processes for the preparation of the compounds of the general formula (I), particularly the compounds of general formulae (Ia) to (Ih).

One such process is for the preparation of a compound of the general formula (Ig):



(Ig)

wherein

R^A, R^B, R^C, R^D, R^E, R^F and n are as defined above in respect of general formula (I) or general formulae (Ia) to (Ih);

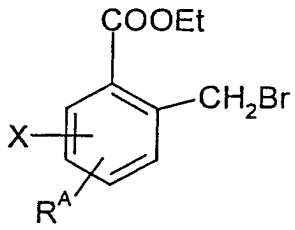
X is as defined above in respect of general formula (Ic) to (Ih);

R^G is selected from: phenyl, piperidinyl and piperazinyl, substituted with at least one substituent selected from: $T(CH_2)_qCR^{23}R^{24}COR^{25}$ (formula 5), OCH_2Phenyl and $-CH_2C(O)\ R^{25}$, wherein T, R^{23}, R^{24}, R^{25} and q are as defined above in

respect of general formula (I) or general formulae (Ia) to (Ih), and optionally at least one further substituent selected from: $-R^5$, -F, -Cl, -Br, -I, -CN, -SCN, -CNO, $-OR^{21}$, $-OC(=O)R^{21}$, $-OS(=O)_2R^{21}$, $-OS(=O)_2NR^{21}R^{22}$, $-OC(=O)OR^{21}$, $-OC(=O)SR^{21}$, $-OC(=O)\ NR^{21}R^{22}$, $-SR^{21}$, $-S(=O)R^{21}$, $-S(=O)_2R^{21}$, -SC(=O)H, $-SC(=O)OR^{21}$, $-NO_2$, $-NR^{21}(OR^{22})$, $-NR^{21}R^{22}$, $-NR^{21}C(=O)R^{22}$, $-N(R^{21})C(=O)OR^{22}$, $-NR^{21}S(=O)_2R^{22}$, $-N[S(=O)_2R^{21}]\ R^{22}$, $C(=O)OR^{21}$, $-S(=O)_2R^{21}$ and $-S(=O)_2OR^{21}$, wherein R^{21} and R^{22} ,which are independent of each other and can be the same or different, are selected from: H, C_1-C_{15} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{15} alkenyl, C_2-C_{15} alkynyl, C_3-C_{15} cycloalkyl, C_4-C_{15} cycloalkylalkyl, monocyclic or polycyclic aryl, C_7-C_{17} arylalkyl and C_3-C_{15} heterocycle; or, in the case of the substituents: $OC(=O)\ NR^{21}R^{22}$ and $-NR^{21}R^{22}$, R^{21} and R^{22}, together with the nitrogen atom to which they are attached, form a saturated, partially saturated, or aromatic heterocycle which optionally contains at least one additional hetero atom selected from: N, O and S; and

W is CH_2 ;

which process comprises alkylating a compound of the formula (II) below:



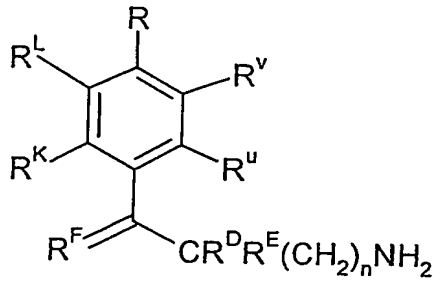
(II)

wherein

R^A is as defined in respect of general formula (I) or general formulae (Ia) to (Ih) above; and

is as defined in respect of general formulae (Ic) to (Ih) above; with

(a) a compound of the formula (III) below:



(III)

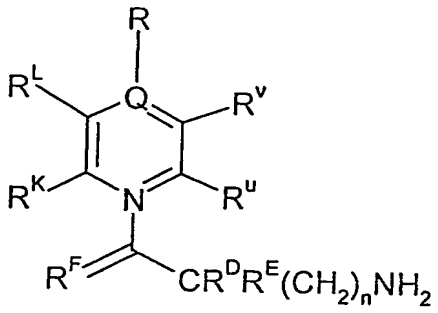
wherein

R is either a group of formula 5: $T(CH_2)_qCR^{23}R^{24}COR^{25}$ (formula 5), wherein T, R^{23}, R^{24}, R^{25} and q are as defined above in respect of general formula (I) or general formulae (Ia) to (Ih), or the group $OCH_2Phenyl$;

R^D, R^E, R^F and n are as defined above in respect of general formula (I) or general formulae (Ia) to (Ih); and

R^L, R^K, R^U and R^V, which are independent and can be the same or different, are selected from the substituents for R^G defined above in respect of general formula (I) or general formulae (Ia) to (Ih); or

(b) a compound of the formula (IV) below:



(IV)

wherein

Q is CH or N;

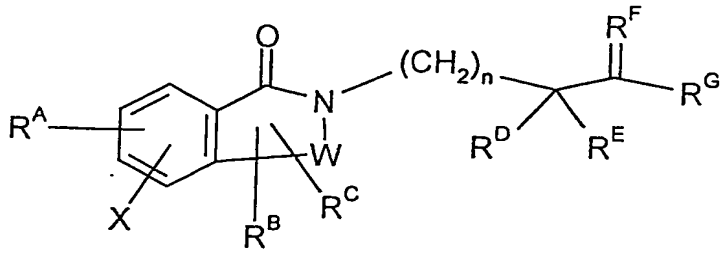
R is either a group of formula 5: $T(CH_2)_qCR^{23}R^{24}COR^{25}$ (formula 5), wherein T, R^{23}, R^{24}, R^{25} and q are as defined above in respect of general formula (I) or general formulae (Ia) to (If), or the group OCH_2Phenyl;

R^D, R^E, R^F and n are as defined above in respect of general formula (I) or general formulae (Ia) to (Ih); and

R^L, R^K, R^U and R^V, which are independent and can be the same or different, are selected from the substituents for R^G defined above in respect of general formula (I) or general formulae (Ia) to (Ih);

in the presence of an organic or inorganic base in an organic solvent, or a mixture of at least two different organic solvents, at a temperature ranging from –40°C to reflux temperature, to effect in situ cyclization to form a compound of the general formula (Ig) above, and, optionally, converting the compound into a physiologically tolerable salt or prodrug.

An alternative process for the preparation of a compound of the general formula (Ig)



(Ig)

wherein

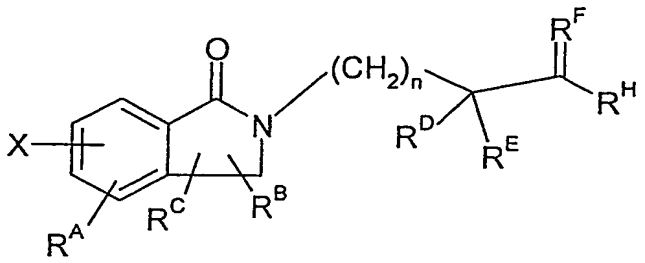
R^A, R^B, R^C, R^D, R^E, R^F and n are as defined above in respect of general formula (I) or general formulae (Ia) to (Ih);

X is as defined above in respect of general formula (Ic) to (Ih);

R^G is selected from: phenyl, piperidinyl and piperazinyl, substituted with at least one substituent selected from: $T(CH_2)_qCR^{23}R^{24}COR^{25}$ (formula 5), OCH_2Phenyl and $-CH_2C(O)\ R^{25}$, wherein T, R^{23}, R^{24}, R^{25} and q are as defined above in respect of general formula (I) or general formulae (Ia) to (Ih), and optionally at least one further substituent selected from: $-R^5$, -F, -Cl, -Br, -I, -CN, -SCN, -CNO, $-OR^{21}$, $-OC(=O)R^{21}$, $-OS(=O)_2R^{21}$, $-OS(=O)_2NR^{21}R^{22}$, $-OC(=O)OR^{21}$, $-OC(=O)SR^{21}$, $-OC(=O)\ NR^{21}R^{22}$, $-SR^{21}$, $-S(=O)R^{21}$, $-S(=O)_2R^{21}$, $-SC(=O)H$, $-SC(=O)OR^{21}$, $-NO_2$, $-NR^{21}(OR^{22})$, $-NR^{21}R^{22}$, $-NR^{21}C(=O)R^{22}$, $-N(R^{21})C(=O)OR^{22}$, $-NR^{21}S(=O)_2R^{22}$, $-N[S(=O)_2R^{21}]\ R^{22}$, $C(=O)OR^{21}$, $-S(=O)_2R^{21}$ and $-S(=O)_2OR^{21}$, wherein R^{21} and R^{22}, which are independent and can be the same or different, are selected from: H, C_1-C_{15} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{15} alkenyl, C_2-C_{15} alkynyl, C_3-C_{15} cycloalkyl, C_4-C_{15} cycloalkylalkyl, monocyclic or polycyclic aryl, C_7-C_{17} arylalkyl, and C_3-C_{15} heterocycle, or, in the case of the substituents: $-OC(=O)\ NR^{21}R^{22}$ and $-NR^{21}R^{22}$, R^{21} and R^{22}, together with the nitrogen atom to which they are attached, form a saturated, partially saturated,

or aromatic heterocycle which optionally contains at least one additional hetero atom selected from: N, O and S; and
W is CH_2;

which process comprises reacting a compound of the formula (V)



(V)

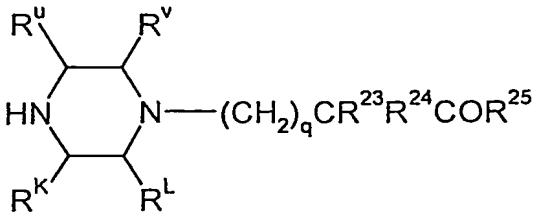
wherein

R^A, R^B, R^C, R^D, R^E, R^F and n are as defined above in respect of general formula (I) or general formulae (Ia) to (Ih);

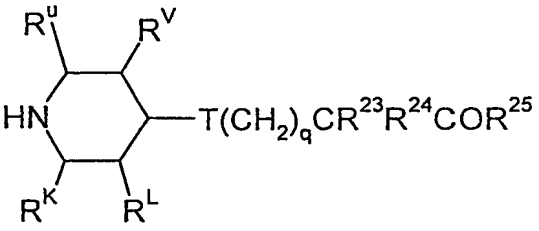
X is as defined above in respect of general formulae (Ic) to (Ih); and

R^H is a halogen, such as Cl ;

with (a) a compound of the formula (VI) or formula (VII) below:



(VI)



(VII)

wherein

R^{23}, R^{24}, R^{25}, T and q are as defined above in respect of general formula (I) or general formulae (Ia) to (Ih);

R^L, R^K, R^U and R^V, which are independent and can be the same or different, are selected from the substituents for R^G defined above in respect of general formula (I) or general formulae (Ia) to (Ih);

in the presence of an organic or inorganic base, to form a compound of the general formula (Ig), wherein R^G is a substituted piperidinyl or piperazinyl ;

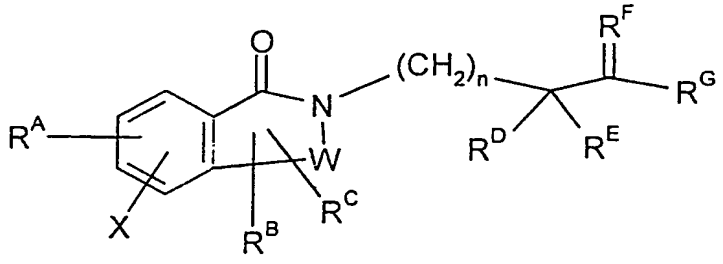
or

(b) a phenyl substituted with at least one hydroxyl, for example, two hydroxyls, and optionally further substituted with at least one group selected from the substituents for R^G defined above in respect of general formula (I) or general formulae (Ia) to (Ih);

to form a compound of the general formula (Ig), wherein R^G is a mono- or poly-substituted phenyl, and optionally converting the compound into a physiologically tolerable salt or prodrug.

Alternatively, a compound of the formula (V) above, wherein R^H is -OH, may be activated by a known procedure by treatment with a mixed anhydride to form a peptide coupling with a compound of the formula (VI) or formula (VII) to provide a compound of the general formula (Ig), wherein R^G is a substituted piperidinyl or piperazinyl.

A further alternative process for the preparation of a compound of the general formula (Ig):



(Ig)

wherein

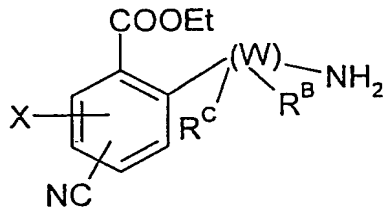
R^A, R^B, R^C, R^D, R^E, R^F and n are as defined above in respect of general formula (I) or general formulae (Ia) to (Ih);

X is as defined above in respect of general formula (Ic) to (Ih);

R^G is phenyl substituted with at least one group selected from: a group of formula 5 and OCH_2Phenyl , wherein formula 5 is: $T(CH_2)_qCR^{23}R^{24}COR^{25}$ in which T, R^{23}, R^{24}, R^{25} and q are as defined above in respect of general formula (I) or general formulae (Ia) to (Ih), and optionally substituted with at least one further substituent selected from: $-R^5$, -F, -Cl, -Br, -I, -CN, -SCN, -CNO, $-OR^{21}$, $-OC(=O)R^{21}$, $-OS(=O)_2R^{21}$, , $-OS(=O)_2NR^{21}R^{22}$, $-OC(=O)OR^{21}$, $-OC(=O)SR^{21}$, $-OC(=O)NR^{21}R^{22}$, $-SR^{21}$, $-S(=O)R^{21}$, $-S(=O)_2R^{21}$, -SC(=O)H, $-SC(=O)OR^{21}$, $-NO_2$, $-NR^{21}(OR^{22})$, $-NR^{21}R^{22}$, $-NR^{21}C(=O)R^{22}$, $-N(R^{21})C(=O)OR^{22}$, $-NR^{21}S(=O)_2R^{22}$, $-N[S(=O)_2R^{21}]R^{22}$, $C(=O)OR^{21}$, $-S(=O)_2R^{21}$ and $-S(=O)_2OR^{21}$, wherein R^{21} and R^{22} may be same or different and are selected from: H, C_1-C_{15} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{15} alkenyl, C_2-C_{15} alkynyl, C_3-C_{15} cycloalkyl, C_4-C_{15} cycloalkylalkyl, monocyclic or polycyclic aryl, C_7-C_{17} arylalkyl, and C_3-C_{15} heterocycle; or , in the case of the substituents: $-OC(=O)NR^{21}R^{22}$ and $-NR^{21}R^{22}$, R^{21} and R^{22}, together with the nitrogen atom to which they are attached, form a saturated, partially saturated, or aromatic heterocycle which optionally contains at least one additional hetero atom selected from: N, O and S; and

W is $-CH_2CH_2-$;

which process comprises alkylating a compound of the formula (VIII):



(VIII)

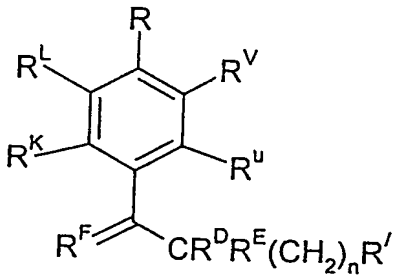
wherein

R^B and R^C are as defined above in respect of general formula (I) or general formulae (Ia) to (Ih);

X is as defined above in respect of general formulae (Ic) to (Ih); and

W is $-CH_2\ CH_2-$;

with a compound of the formula (IX)



(IX)

wherein

R is a group of the formula: $T(CH_2)_qCR^{23}R^{24}COR^{25}$ (formula 5), wherein T, R^{23}, R^{24}, R^{25} and q are as defined above in respect of general formula (I) or general formulae (Ia) to (Ih);

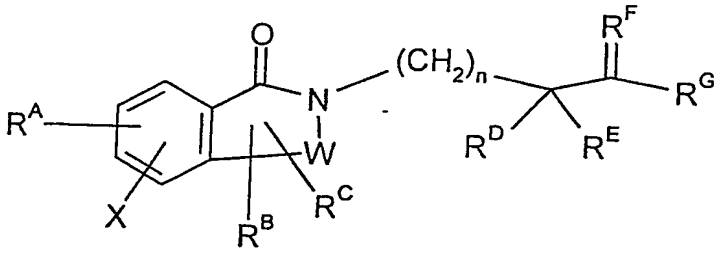
R^D, R^E, R^F and n are as defined above in respect of general formula (I) or general formulae (Ia) to (Ih);

R^L, R^K, R^U and R^V, which are independent and can be the same or different, are selected from the substituents for R^G defined above in respect of general formula (I) or general formulae (Ia) to (Ih) above; and

R' is a leaving group;

in the presence of an organic or inorganic base in a solvent, or mixture of at least two solvents, to effect in situ cyclization to form a compound of the general formula (Ig) above, and, optionally, converting the compound into a physiologically tolerable salt or prodrug.

A yet further alternative process for the preparation of a compound of the general formula (Ig):



(Ig)

wherein

R^A, R^B, R^C, R^D, R^E, R^F and n are as defined above in respect of general formula (I) or general formulae (Ia) to (Ih);

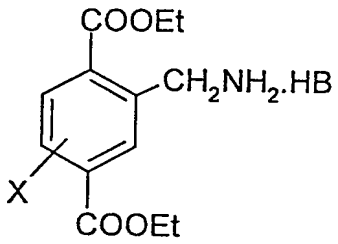
X is as defined in respect of general formula (Ic) to (Ih) above;

R^G is phenyl, having at least one substituent which is OCH_2Phenyl, and optionally at least one further substituent selected from: $-R^5$, -F, -Cl, -Br, -I, -CN, -SCN, -CNO, $-OR^{21}$, $-OC(=O)R^{21}$, $-OS(=O)_2R^{21}$, $-OS(=O)_2NR^{21}R^{22}$, $-OC(=O)OR^{21}$, $-OC(=O)SR^{21}$, $-OC(=O)\ NR^{21}R^{22}$, $-SR^{21}$, $-S(=O)R^{21}$, $-S(=O)_2R^{21}$, $-SC(=O)H$, $-SC(=O)OR^{21}$, $-NO_2$, $-NR^{21}OH$, $-NR^{21}(OR^{22})$, $-NR^{21}R^{22}$, $-NR^{21}C(=O)R^{22}$, $-N(R^{21})C(=O)OR^{22}$, $-NR^{21}S(=O)_2R^{22}$, $-N[S(=O)_2R^{21}]\ R^{22}$, $C(=O)OR^{21}$, $-S(=O)_2R^{21}$ and $-S(=O)_2OR^{21}$, wherein R^{21} and R^{22} , which are

independent and can be the same or different, are selected from: H, C_1-C_{15} alkyl, partially or fully fluorinated C_1-C_{10} alkyl, C_2-C_{15} alkenyl, C_2-C_{15} alkynyl, C_3-C_{15} cycloalkyl, C_4-C_{15} cycloalkylalkyl, monocyclic or polycyclic aryl, C_7-C_{17} arylalkyl and C_3-C_{15} heterocycle; or , in the case of the substituents: -OC(=O) $NR^{21}R^{22}$ and -$NR^{21}R^{22}$, R^{21} and R^{22}, together with the nitrogen atom to which they are attached, form a saturated, partially saturated, or aromatic heterocycle which optionally contains at least one additional hetero atom selected from: N, O and S; and

W is $-CH_2-$;

which process comprises, alkylating a compound of the formula (X)



(X)

wherein X is as defined above; and

B is halogen, acetate, formate etc.

with a compound of the formula:

$R^G (C=R^F)CR^DR^E(CH_2)nL$

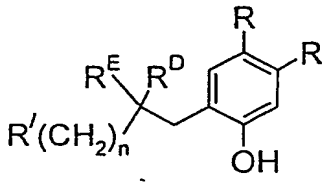
wherein

R^D, R^E, R^F, R^G and n are as defined; and

L is a leaving group;

in the presence of an organic or inorganic base in a solvent, or mixture of at least two solvents, to effect in situ cyclization to form the compound of general formula (Ig) above, and, optionally, converting the compound into a physiologically tolerable salt or prodrug.

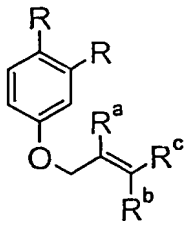
The present invention further relates to novel intermediates identified below as: H63, G48, G54 and H69, required for the synthesis of the compounds of general formula (I) or general formulae (Ia) to (Ih), and to novel processes for the preparation of said intermediates. Accordingly, the present invention provides a novel process for the preparation of the novel intermediate H-63:



H-63

wherein R is $T(CH_2)_qCR^{23}R^{24}COR^{25}$ in which T, q, R^{23}, R^{24}, R^{25} are as defined in respect of general formula (I) or general formulae (Ia) to (Ih); R' is H , a protected amino group, such as NHZ, or L, wherein L is a leaving group, such as halogen, OMes, OTs or NHZ; R^D and R^E are as defined in respect of general formula (I) or general formulae (Ia) to (Ih),

which process comprises reacting the O-allylic compound H-60

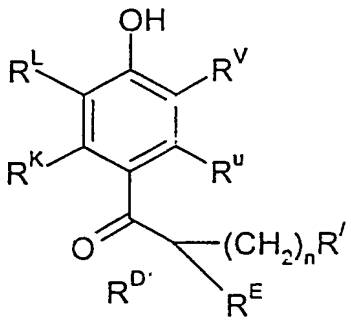


H-60

wherein R^a, R^b and R^c , which are independent and can be the same or differerent, are selected from: C_1-C_5 alkyl and C_7-C_{12} alkylaryl , and R has the meaning defined above, with the compound $R'(CH_2)_nCR^DR^ECOCl$, wherein R', R^D , R^E and n are as defined above, in the presence of a Lewis acid catalyst, such as Zn, BF_3.etherate, $FeCl_3$, $AlCl_3$ and $ZnCl_2$, preferably Zn, and in the presence of a solvent or mixture of at least two solvents selected from, for example: toluene, benzene, heptane, kerosene, CS_2, CCl_4 and nitrobenzene, preferably toluene.

This is a single step process in which the O-allylic compound H60 may undergo cleavage during the reaction.

The present invention also provides a novel process for the preparation of novel intermediates G48, G54 and H69 required for the synthesis of a compound of the general formula (I) or general formulae (Ia) to (Ih):



G48/G54/H69

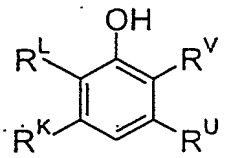
wherein

R^K, R^L, R^V and R^U, which are independent and can be the same or different, are selected from the substituents of R^G as defined in respect of general formula (I) or general formulae (Ia) to (Ih), with the proviso that at least one of the groups R^K, R^L, R^V and R^U is OH;

R' is a protected amino group, such as NHZ, NHTroc or NHFmoc, preferably NHZ;

R^D, R^E and n are as defined in respect of general formula (I) or general formulae (Ia) to (Ih);

which process comprises reacting a mono- or polyhydroxy phenol of the formula (XI):



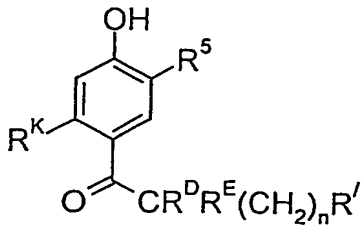
wherein R^K, R^L, R^V and R^U have the meaning defined above,

with a compound of the formula: $R'(CH_2)_nCR^DR^ECN$ (formula XII), in which R', R^D and R^E & n have the meaning defined hereinabove,

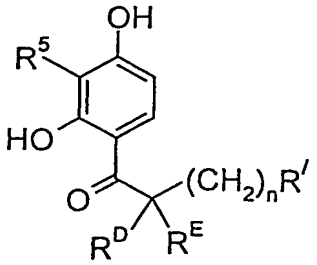
in the presence of an inorganic acid, such as HCl or HBr, and a Lewis acid, such as Zn, BF_3.etherate, $FeCl_3$, $AlCl_3$ or $ZnCl_2$, preferably $ZnCl_2$.

The reaction may be carried out at 0°C to 60°C, preferably at 0°C to ambient temperature, in at least one solvent selected from, for example: ether, benzene, THF and dioxane, preferably ether.

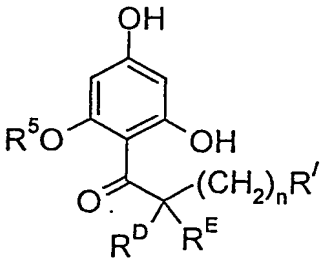
The novel intermediates G-48, G-54 and H-69 are given below:



G-48



G-54

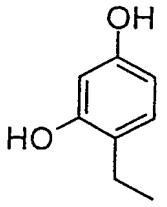


H-69

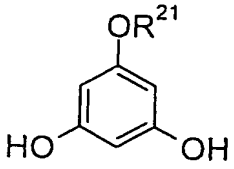
wherein

R^K, R^5, R', R^D, R^E & n have the meaning defined hereinabove.

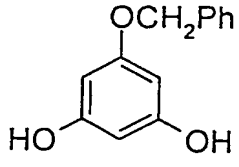
Examples of the polyhydroxy phenol that may be used in the process of the present invention are the intermediates G-47, H-65 and H-68, given below:



G-47



H-65



H-68

wherein R^{21} is as defined in respect of general formula (I) or general formulae (Ia) to (Ih). Specific examples of the polyhydroxy phenol include: 2 or 4 substituted resorcinol, 1,2,3 trihydroxyphenol, 1,2,4 trihydroxyphenol and 1,3,5 trihydroxyphenol.

SYNTHESIS

The compounds of the present invention can be synthesized by the methods described below, with reference to the schemes in Figures A-H, J and K. Some steps in the methods may include synthetic methods known in the art of synthetic organic chemistry or a modification thereof, as appreciated by those skilled in the art. However, the methods of preparation of the compounds of the present invention are not limited to those methods described below. The reactants and intermediates used in the processes described are either commercially available or can be prepared according to standard literature procedures.

All references cited here are hereby incorporated in their entirety herein by reference.

The following abbreviations are used herein:

AcOH:	acetic acid
Ac_2O:	acetic anhydride
AIBN:	2,2′-azobis-(2-methylpropionitrile) /2,2′-azobisisobutyronitrile
β-Ala:	3-aminopropionic acid
Boc:	*tert*-butyloxycarbonyl
Boc_2O:	di-*tert*-butyl dicarbonate
DCC:	1,3-dicyclohexylcarbodiimide

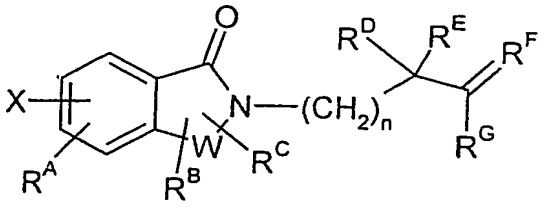
DCU:	1,3-dicyclohexyl urea
DEA:	diethyl amine
DIEA	diisopropylethyl amine
DMAP:	4-dimethylaminopyridine
DMF:	N,N-dimethylformamide
DMSO:	dimethylsulfoxide
EtOAc:	ethyl acetate
EtOH:	ethyl alcohol
Fmoc:	Fluorenyl methyloxy carbonyl
HOBt:	1-hydroxybenzotriazole
IBCF:	*iso*-butylchloroformate
IPA	iso-propyl alcohol
mCPBA	meta-chloroperbenzoic acid
MeOH:	methanol
NBS:	N-bromosuccinimide
NCS:	N-chlorosuccinimide
NIS:	N-iodosuccinimide
NMM:	N-methylmorpholine
NMP:	N-methylpyrrolidine
PPh_3:	triphenylphosphine
PTSA:	4-toluenesulfonic acid
Pyr:	pyridine
TEA:	triethylamine
TFA:	trifluoroacetic acid
THF:	tetrahydrofuran
Troc	2,2,2-trichloroethoxycarbonyl
Tyr:	L-tyrosine
Z:	benzyloxycarbonyl

The symbols used herein R^1 to R^{25}, R^A, R^B, R^C, R^D, R^E, R^F, R^G, M, B, n, q, W and T have the same meaning as described for the general formula (I) or general

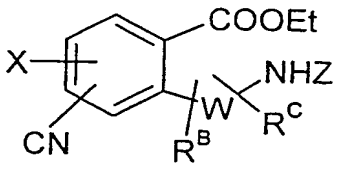
formulae (Ia) to (Ih), unless otherwise indicated; L is a leaving group such as halogen, OMe or OTs; Q is CH or N. For the purpose of describing the synthesis, X_1, X_2 and X_3 are replaced by X; Y^1 and Y^2 together, are = O; R is $T(CH_2)_qCR^{23}R^{24}COR^{25}$; and R' is H, a leaving group (L) or a protected amine, such as -NHZ.

A convenient method for the synthesis of compounds of the present invention involves alkylation of an appropriately substituted amino compound with a suitable alkylating agent and in situ cyclization followed by reaction steps involving functional group modification. Examples of similar cyclization steps have been described in US –A-5 719 144.

Compounds of general formula (I) above may be derived from key intermediates designated as A-8/B-20 and B-19. The preparation of these intermediates by alternative reaction sequences are depicted in the schemes shown in Figures A (compound A-8) and B (compounds B-19 and B-20), which are provided in the accompanying drawings.



A-8 / B-20



B-19

Figure A

The preparation of variants of the key intermediate A-8 by alternative reaction sequences are described in the following processes designated herein as processes 1-1, 1-2, 1-3 and 1-4, which are schematically presented in Figure A.

Process 1-1 for the preparation of compound A-8 (R^A is NO_2, R^B and R^C are absent, X is H)

(i) An appropriately substituted o-tolylamine may be subjected to a Sandmeyer reaction (Vogel's Textbook of Practical Org. Chem., 5th edition, 938) to obtain the corresponding cyano compound, which may be hydrolysed with 50-75% aqueous H_2SO_4 at 100°-150°C for 12-24 hrs in accordance with a known procedure (Vogel's Textbook of Practical Org. Chem., 5th edition, 1063). The resulting acid may further be converted to its corresponding ester designated as A-1 by any standard procedure known in the art. Alternatively, ester A-1 may also be obtained from the cyano compound by alcoholysis in presence of a mineral acid under reflux.

(ii) The methyl group in A-1 may be converted to CH_2L (wherein L represents a leaving group, e.g. Br), by any conventional method known in the art. One suitable method for said conversion involves treating the ester A-1 with NBS in presence of AIBN or dibenzoyl peroxide under reflux in an organic solvent, such as carbon tetrachloride, chloroform or carbon disulphide, for 2-24 h to obtain the compound designated as A-2.

(iii) The resulting compound A-2 may then be converted to the desired compound A-8 (R^A is NO_2, R^B and R^C are absent, W is CH_2) by alkylation followed by in situ cyclization with compounds designated herein as H-72, J-77 and K-84. Said cyclization step may be carried out in presence of an organic base, such as TEA, DIEA or pyridine, or an inorganic base, such as $NaHCO_3$, Na_2CO_3, $KHCO_3$, K_2CO_3, Cs_2CO_3, or CsOH, in an organic solvent, such as CH_2Cl_2, $CHCl_3$, MeOH, EtOH, iPrOH, THF, dioxane or DMF, or a mixture of at least two of said solvents, at a temperature ranging from –40°C to reflux; preferably at –25°C to ambient temperature.

The synthesis of the compounds H-72, J-77 and K-84 are described hereinafter

in processes 8-2, 9-1 and 10-1, respectively.

Process 1-2 for the preparation of compound A-8 (R^A is CN, R^B and R^C are absent, X is H) :

(i) The nitro group in the ester A-1 may be reduced to the corresponding amine designated as A-3 by catalytic hydrogenation or transfer hydrogenation with ammonium formate in presence of a catalyst, such as Pd, Pt, Pd-C or Pt-C, or with Raney Ni, in an organic solvent such as EtOAc, MeOH, EtOH, iPrOH, DMF, or a combination of at least two of said solvents. This reduction may also be carried out by various conventional methods known in the art for converting a nitro group to an amino group. One suitable method uses Zn and $CoCl_2.6H_2O$ as described in a reported procedure (Ind. J. Chem., 1994, 33B, 758).

(ii) The amino group in compound A-3 may then be converted to a cyano group by a Sandmeyer reaction (Vogel's Textbook of Practical Org. Chem., 5th edition, 938). The resulting compound may be subsequently converted to compound A-4 in a manner similar to that described hereinabove for the conversion of compound A-1 to compound A-2.

(iii) The compounds H-72, J-77 and K-84 may be subjected to alkylation and in situ cyclization with compound A-4 by a procedure as described hereinabove for the conversion of compound A-2 to the desired compound A-8 (R^A is CN).

Process 1-3 for the preparation of variants of compound A-8 (R^A is CN, R^B and R^C are absent, X is COR^{10}, OR^{10}, C_1-C_{15}-alkyl , halogen, SR^{10}, $S(O)R^{10}$, $S(O)_2R^{10}$, $NHCOR^{10}$, $NHCOOR^{10}$, NO_2, or NHZ/NHTroc):

(i) Preparation of variants of compound A-5:

a) The compound A–5 (X is COR^{10}) may be prepared by first protecting the amino group in compound A-3 with an appropriate

protecting group (eg. phthaloyl) and then subjecting the resulting compound to Friedel-Crafts acylation with a suitable acylating agent, such as an acid chloride or an anhydride, followed by deprotection of the amino group by any conventional method known in the art.

b) The compound A–5 (X is C_1-C_{15}-alkyl) may be prepared by first protecting the amino group in compound A-3 with an appropriate protecting group (eg. phthaloyl) and then subjecting the resulting compound to Friedel-Crafts alkylation followed by deprotection of the amino group. Alternatively, said compound A-5 may be prepared by reducing the carbonyl group in the compound of the type A-5 (wherein X is CO C_1-C_{14}-alkyl) , which after reduction results in CH_2 C_1-C_{14}-alkyl, according to a reported procedure (Synthesis, 763, 1978; Tetrahedron, 23, 2235, 1967).

c) The compound A-5 (X is halogen, such as Cl, Br, I) may be prepared by treating compound A-3 with N-halosuccinimide in an organic solvent, such as DMF, acetonitrile, AcOH, $CHCl_3$, CS_2, CH_2Cl_2 or a mixture of at least two of said solvents, at a temperature ranging from 0°-100°C.

d) The compound A-5 (X is OR^{10}) may be prepared by first protecting the amino group in the compound A-5 (X is Cl, Br or I) with a suitable protecting group. such as Boc or Z, and subsequently treating the resulting compound with an alkali metal alkoxide in the presence of CuCl, CuBr or CuI in accordance with a reported procedure (Tetrahedron, 48, 3633, 1992; J. Org. Chem., 62, 5413, 1997), followed by deprotection of the amino group.

e) Compound A-5 (X is SR^{10}) may be prepared by treating the compound A-5 (X is Cl, Br or I) with $CuSR^{10}$ in accordance with a reported procedure (J.Am.Chem.Soc, 81, 4927, 1959). The resulting compound A-5 (X is SR^{10}) may be converted to its corresponding sulfoxide or sulfone [X is $S(O)R^{10}$ or $S(O)_2R^{10}$] by subjecting it to oxidation.

f) Compound A-5 (X is NO_2) may be prepared by first protecting the amino group in compound A-3 with a suitable protecting group (e.g. phthaloyl) and subjecting the resulting compound to a standard nitration reaction followed by deprotection of the amino group by any conventional method known in the art.

Alternatively, prior to deprotection, the nitro group in the resulting compound may be reduced to the corresponding amino group by following the same procedure as described hereinabove for the conversion of compound A-1 to compound A-3. The newly formed amino group may be protected with a different protecting group, such as Z or Troc, so that it is compatible with the phthaloyl group and does not interfere at the time of deblocking the phthaloyl protecting group. The phthaloyl group may then be removed to obtain the corresponding compound A-5 (X is NHZ or NHTroc).

Alternatively, the amino compound prior to deprotection of phthaloyl group may be treated with an appropriate acid chloride or a choloroformate using a standard procedure in the art to obtain the desired compound A-5 (X is $NHCOR^{10}$ or $NHCOOR^{10}$).

(ii) The thus obtained variants of compound A-5 may be converted to the corresponding compound A-6 by a procedure as described hereinabove for the conversion of compound A-3 to compound A-4.

(iii) The compounds H-72, J-77 and K-84 may be subjected to alkylation and in situ cyclization with compound A-6 by a procedure as described above in process 1-1, to obtain the desired compound A-8 (R^A is CN, R^B and R^C are absent, X is as defined above).

(iv) Alternatively, the compound A-8 may also be obtained from compound A-7 which in turn can be obtained from compound A-6. The -CH_2Br group in compound A-6 may be converted to -CH_2CN or –$CH_2CH_2NO_2$ by using any conventional method. One such method for converting the -CH_2Br group to -CH_2CN is by treating the halide with an alkali metal cyanide or $Zn(CN)_2$ in a suitable solvent, such as DMF, DMSO or alcohol. One method for converting the -CH_2Br group to –$CH_2CH_2NO_2$ is by treating the halide with nitro methane in the presence of a suitable base, such as NaOEt or NaH. The nitrile or nitro group is then reduced to an amino group by any conventional method known in the art. One such method involves catalytic hydrogenation as described hereinabove to obtain the compound A-7.

The resulting compound A-7 may then be converted to the desired variants of compound A-8, wherein W is CH_2CH_2 and other symbols are as defined earlier, by alkylation followed by in situ cyclization with compounds designated herein as F-46, G-53, H-63, wherein R' is a leaving group, such as Cl, Br, I, OMes and OTs, and J-74. The synthesis of the compounds F-46, G-53, H-63 and J-74 are described hereinafter in processes 6-1, 7-1, 8-1 and 9-1, respectively.

Process 1-4 for the preparation of other variants of compound A-8:

(i) The intermediates A-2, A-4 and A-6 may alkylate amines of the type $H_2N(CH_2)_nCR^DR^ECOOR^1$ (wherein R^1 is Me/Et/CH_2Ph) followed by cyclization to obtain a compound designated as A-9. Likewise, the intermediate A-7 may undergo alkylation with $L(CH_2)_nCR^DR^ECOOR^1$ to obtain the compound A-9.

(ii) The compound A-9 may be hydrolysed with aqueous LiOH in an organic solvent, such as MeOH, EtOH, iPrOH, THF, dioxane and DMF, to obtain the corresponding acid A-10. The protecting group (R^1) of the ester, such as the benzyl group, may also be removed by catalytic hydrogenolysis of A-9 to obtain the corresponding acid A-10.

(iii) The acid thus obtained may then be coupled with compounds designated as K-81 or K-83 via a standard peptide coupling procedure, preferably with DCC, by a mixed anhydride method or by using any other method for activation of the acid to give further variants of compound A-8.

(iv) Alternatively, the acid A-10 may further be converted to its acid chloride A-11 by any conventional method, for example, by treating said acid with $SOCl_2$. The thus obtained acid chloride may be coupled with compounds designated as K-81 or K-83 in the presence of organic bases, such as TEA, pyridine or DIPEA and inorganic bases such as NaOH, Na_2CO_3, or $CsCO_3$. The synthesis of the compounds K-81 and K-83 are described hereinafter in process 10-1.

(v) Alternatively, a suitably substituted mono or polyhydroxy phenol derivative, such as H65, H68 and G47, may be subjected to a Friedel-Crafts acylation with the acid chloride A-11 using a Lewis acid catalyst or by using activated Zn as reported in the literature (Synth. Commun, 28, 2203, 1998), to obtain yet another variant of compound A-8.

Figure B

The preparation of variants of the key intermediate B-19 and B-20 by alternative reaction sequences is described below by the processes designated as processes 2-1, 2-2, 2-3 and 2-4, which are schematically presented in Figure B:

Process 2-1 for the preparation of compound B-20 (X is H):

(i) 4-Methylbenzoic acid may be treated with bromine in presence of $AgNO_3$ according to a reported method (J. Org. Chem., 25, 1024, 1960) to obtain 3-bromo-4-methylbenzoic acid. The methyl group in the resulting compound may be oxidized by any conventional oxidizing agent, for example, alkaline potassium permanganate at a temperature ranging from 50°-100°C for 2-6 hr to obtain the corresponding dicarboxylic acid. The resulting dicarboxylic acid (Beil, 9, IV, 3335) may be esterified by refluxing with an appropriate alcohol (e.g. EtOH) in presence of a mineral acid or by treatment with $SOCl_2$ followed by addition of an appropriate alcohol (e.g. EtOH) to give a compound designated as B-12.

(ii) The bromo compound B-12 may then be converted to a cyano compound by treating it with a reagent, such as CuCN, alkali metal cyanide or $Zn(CN)_2$; in a solvent, such as pyridine, DMF, a lower alcohol, or pyrrolidone; at a temperature ranging from 50°-150°C for 3-24 hr. The resulting cyano compound may then be subjected to catalytic hydrogenation in a solvent, such as an alcohol, AcOH, chloroform, DMF, or a mixture of at least two of said solvents, at 200-500 psi, preferably in an alcohol and chloroform mixture over PtO_2 at 400 psi for 2-8 hr to obtain a compound designated as B-13, wherein B is, for example, halogen, acetate or formate.

(iii) The compound B-13 may then be subjected to alkylation with $R^G(C=R^F)CR^DR^E(CH_2)_nL$ and in situ cyclization to obtain a compound designated as B-16, wherein the groups R^K, R^L, R^U and R^V are the same as the ring substituents in the definition of R^G. In compound B-16, R^G is not substituted with a –COOR group. The ester group (R^A= -COOEt) in compound B-16 may be converted to a cyano group by any conventional method, for example, through amide formation followed by dehydration by

a number of reagents well known in the art, to obtain a compound designated as B-17, wherein R^A= -CN.

Alternatively, the ester group (R^A) in the compound B-16 may be converted to a -$(CH_2)_pCN$ group by a number of synthetic steps. These steps involve hydrolysis of an ester to an acid, reduction of the resulting acid to an alcohol by any conventional reducing agent, such as $NaBH_4$ - mixed anhydride (except in cases in which R^F is O and S). The resulting alcohol is converted to a leaving group such as halide, mesyl or tosyl, by a standard procedure well known to those skilled in the art. This is followed by treatment with alkali metal cyanide by a known procedure. (Vogel's Textbook of Practical Org. Chem, 5th edition, 714).

The benzyl group of B-16 to B-18 can be removed by a known method such as catalytic hydrogenolysis or by treatment with silyl iodide particularly in those compounds wherein R^F is O, in a solvent such as CH_2Cl_2, $CHCl_3$, DMF, benzene, toluene, THF or dioxane, at ambient to reflux temperature for 2-18 hr.

(iv) The phenolic OH group formed by the removal of the benzyl group in B-16 to B-18 may be finally coupled with L- $(CH_2)_qCR^{23}R^{24}COR^{25}$ by a standard procedure to afford the desired key intermediate B-20 (where R^A = –$(CH_2)_pCN$).

<u>Process 2-2 for the preparation of variants of compound B-20 (X is COR^{10}, C_1-C_{15}-alkyl, halogen, OR^{10}, SR^{10} , $S(O)R^{10}$ or $S(O)_2R^{10}$, NO_2, $NHC(O)R^{10}$, $NHC(O)OR^{10}$, NHZ or NHTroc)</u> :

(i) The preparation of variants of compound B-13 (X is COR^{10}, OR^{10}, SR^{10}, $S(O)R^{10}$ or $S(O)_2R^{10}$)

The variants of compound B-13 may be prepared by functionalising 3-bromo-4-methylbenzoic acid by X, wherein X has the meaning as described above, in a manner similar to that described in process 1-3 for the preparation of variants of compound A-5.

(ii) The variants of compound B-13 may then be converted to the desired variants of compound B-20 in a manner similar to that described in the above process 2-1.

Process 2-3 for the preparation of compound B-20 starting from nitro 2-halobenzoic acid:

(i) Nitro substituted 2-halobenzoic acid may be esterified in a manner similar to that described in the above process 2-1(i).

(ii) The halo group in the resulting ester may then be converted to the cyano group according to the procedure described in process 2-1(ii). Both the nitro and the cyano groups may then be reduced under acidic conditions by any conventional method known in the art, for example, catalytic hydrogenation as described in the above process 2-1.The primary amino group can selectively be protected using a suitable protecting group, such as Z, Boc, Fmoc or Troc , to give B-14.

(iii) In yet another variation, the substituted 2-halo benzoate ester may be treated with a reagent, such as $ZNH\text{-}CH_2CR^B{=}CR^C\text{-}L$, in the presence of a Pd- or Ni- based catalyst. This can be followed by reduction of the nitro group and double bond to give another variant of B-14. The reduction of the double bond is optional.

(iv) Similarly, the substituted 2-halo benzoate ester may be treated with $R^PO\text{-}CR^B{=}CR^C\text{-}L$. Removal of the protecting group (R^P) from the resulting enol ether will give a keto compound. The keto compound may undergo

reductive amination to obtain a diamine. The amino group in the side chain may be protected selectively, using reagents such as Z, Fmoc or Troc, to give further variants of compound B-14.

(v) The variants of compound B-14 thus obtained may be subjected to a Sandmeyer reaction in a manner similar to that described in process 1-2 with the minor modification of carrying out said reaction in a solvent medium of an organic solvent, such as THF, dioxane or DMF, and water to obtain a compound designated as B-15.

(vi) The compound B-15 may then be reacted with TFA-thioanisole (J.C.S. Chem. Commun. 101, 1980) or any other standard reagent used for deprotection such as 2N HBr in AcOH for the removal of the Z group to obtain a compound designated as B-19.

(vii) The resulting compound B-19 may then be converted to the desired key compound B-20 by alkylation followed by in situ cyclization with compounds F-46 (R' is L), G-53 (R' is L), H-63(R' is L), H-71(R' is L), and J-74. The symbol L represents a leaving group, such as Cl, Br, I, OMes or OTs.

The synthesis of said fragments F-46, G-53, H-63, H-71 and J-74 are provided hereinafter in processes 6-1, 7-1, 8-1 and 9-1, respectively.

<u>Process 2-4 for the preparation variants of compound B-20 starting from nitro 2-halobenzoic acid (X is $C(O)R^{10}$, OR^{10}, halogen, SR^{10}, NO_2, $NR^{10}R^{11}$, $NHCOR^{10}$ or $NHCOOR^{10}$)</u>

(i) The compound B-14 described above may be substituted with X (which is as described above) by the method described in process 1-3. For this, B-14 may be used in which the amino group substituted on the phenyl ring may be in the unprotected or protected (with groups, such as

phthaloyl, Fmoc or Troc, which are compatible with Z) form. (Protecting groups in Org Synthesis, Ed, III, Green. T.W. and Wuts. P.G.M., John Wiley & Sons Inc., p 494). Subsequent to the substitution of compound B-14 with X, any protecting group, such as phthaloyl, Fmoc or Troc, may be removed by any conventional method.

(ii) The resulting amine may be subjected to a Sandmeyer reaction as described in process 1-1 to obtain a cyano derivative which on deprotection would result in another variant of B-19.

(iii) The resulting compound may then be converted to the desired variant of compound B-20 by alkylation with compounds F-46 (R' is L), G-53 (R' is L), H-63 (R' is L), H-71 (R' is L), and J-74, followed by in situ cyclization. The symbol L is as described earlier.

The synthesis of said compounds F-46, G-53, H-63, H-71 and J-74 are provided hereinafter in processes 6-1, 7-1, 8-1 and 9-1, respectively.

The key compounds A-8, B-20, A-9 and B-15 thus obtained may be subjected to further reaction steps to obtain the compounds designated herein as C-22 and C-23; D-25, D-26, D-27 and D-28; and E-32 and E-33; which correspond to the compounds of general formula (I), including those of general formulae (Ia) to (Ih), as described below by the processes 3-1 to 5-1 and as schematically presented in Figures C, D and E, respectively.

Figure C

The preparation of compounds C-22 and C-23 by alternative reaction sequences is described below by the processes designated as process 3-1 and process 3-2, which are schematically presented in Figure C:

Process 3-1 for the preparation of compounds C-22 and C-23 :

(i) The cyano group in compound A-8 (R^A = -CN) or B-20 (R^A = $NC(CH_2)_p$) may be subjected to a Pinner reaction to obtain the corresponding hydrochloride salt of an imino ether which may then be treated with an appropriate amino compound (substituted or unsubstituted) to obtain the substituted or unsubstituted amidine compound designated as C-21. Likewise the imino ether may be treated with a substituted or unsubstituted hydroxylamine to obtain the corresponding substituted or unsubstituted oxime designated as C-22.

Alternatively, the cyano group in compound A-8 (R^A = -CN) or B-20 (R^A = $NC(CH_2)_p$) may be subjected to a known reaction (Daniel. J., Sall. et. al. Bioorg. Med. Chem. Lett. 6, 81, 1996 and reference therein) to obtain the corresponding thioimidate compound which may then be treated with an appropriate amino compound (substituted or unsubstituted) or hydroxylamine to obtain the respective substituted or unsubstituted amidino compound C-21 or the oxime C-22.

Compounds of the present invention wherein the group R^G in the compound C-23 (corresponding to compounds of general formulae (I), (Ia) to (Ih)) is substituted by a group of formula 5 (defined hereinabove) in which R^{25} is OH may be obtained as follows: (1) by subjecting an appropriately substituted oxime C-22 (R^{25} is OCH_2Ph) to acylation with Ac_2O (R^{25} is OMe/OEt) followed by hydrogenation (R^{25} is OH) in accordance with a known procedure (D. C., Batt. et. al. J. Org. Chem. 65, 8100, 2000), (2) by hydrogenolysis of an appropriately substituted amidine C-21 (R^{25} is OCH_2Ph), or (3) by first protecting the amidino group with an appropriate group, preferably a Boc group, to give the compound C-23 (R^{25} is OMe/OEt, R^3 is Boc) which may be subjected to hydrolysis followed by deprotection of the amidino group (R^{25} is OH; R^3 is H) using any conventional method known in the art .

A variant of compound C-22 (R^1 &/or R^4 is H, and R^{25} is OH) may be obtained by hydrolysis of an appropriately substituted hydroxy amino compound C-22 (R^1 &/or R^4 is H, and R^{25} is OMe or OEt) by LiOH in aqueous THF or NaOH or KOH in MeOH or a lower alcohol.

Yet another variant of compound C-23 ($R^1/R^3/R^4$ is $COOR^5$ or $COSR^5$) may be prepared by treating a suitably substituted amidine C-21 (in which at least one of R^1, $R^3$and R^4 in formula 3 as defined under general formula (I) or general formulae (Ia) to (Ih) represents H) with a suitable chloroformate (R^5OCOCl or R^5SCOCl) or dicarbonate ($(R^5OCO)_2O$ or $(R^5SCO)_2O$).

Yet another variant of compound C-23, namely the N-sulphonyl or N-acyl derivative of said compound, may be obtained by treating a suitably substituted amidine C-21 (in which at least one of R^1, R^3 and R^4 in formula 3 as defined under general formula (I) or general formulae (Ia) to (Ih) represents H) with a suitable sulfonyl chloride or acyl chloride,respectively.

Yet another further variant of compound C-23, namely the carbonate, O-acyl or O-sulfonyl derivative of said compound, may be prepared by treating the oxime C-22 (in which at least one of R^1 or R^4 in formula 3 as defined under general formula (I) or general formulae (Ia) to (Ih) represents OH) with an appropriate reagent such as chloroformate, acyl chloride or sulfonyl chloride.

<u>Process 3-2 for the preparation of compounds C-22 and C23, wherein the R^A group represents a heterocyclic ring :</u>

The compound C-23 (R^A is 1,2,4-oxadiazole) may be prepared by cyclizing compound C-22 (R^1 &/or R^4 is H) with a suitable acid anhydride, such as acetic anhydride, in accordance with a reported procedure (Joachim

Gante et al, Bioorg. Med. Chem. Lett. 6, 2425, 1996) followed by hydrolysis.

Likewise, another compound corresponding to compound C-22 (R^A is 5-oxo-4,5-dihydro-[1,2,4]oxadiazole)may be prepared by treating the compound C-22 (R^1 &/or R^4 is H) with a reagent such as diethyl carbonate, carbonyl diimidazole, triphosgene or phosgene by using a standard procedure known in the art .

Figure D

The preparation of compounds D-25 and D-28 by alternative reaction sequences is described below by the processes designated as process 4-1, which are schematically presented in Figure D:

Process 4-1 for the preparation of compounds designated as D-25 to D-28

(i) The nitro group in the compound A-8 (R^A is NO_2) may be subjected to reduction as described hereinbefore by using Zn and $CoCl_2$ (Baruah. R. N., Ind. J. Chem., 33B, 758, 1994) to obtain the corresponding amino compound designated as D-24.

(ii) The amino compound D-24 may be treated with a suitable ω-di-halogen compound under standard conditions known in the art to give the compound designated as D-25 which corresponds to a cyclic amino derivative.

(iii) The amino compound D-24 may also be substituted with a desired alkyl group to give a compound designated as D-26.

(iv) The amino compound D-24 may further be treated with a suitably substituted thioimidate salt (Ting Su et al, J. Med. Chem., 40, 4308, 1997) to obtain a variant of the amidine compound designated as D-28, in which R^A represents the group of formula 4 (defined hereinabove).

The amidine compound D-28 wherein at least one of the groups R^7 and R^9 in formula 4 represents H, may further be functionalised with groups such as urethan, N-acyl or N-sulfonyl by treating with a suitable chloroformate, acyl chloride or sulfonyl chloride, respectively, to obtain the desired variants of the compound D-28.

Figure E

The preparation of compounds E-32 and E-33 by alternative reaction sequences is described below by the processes designated as process 5-1 and process 5-2 which are schematically presented in Figure E:

Process 5-1 for the preparation of compounds designated as E-32 and E-33 starting from compound A-9:

(i) The 1,2,4-oxadiazole derivative designated as E-29 can be obtained from compound A-9 by a procedure which is described in process 3-2 above. The 1,2,4-oxadiazole derivative E-29 may be treated with a compound designated as K-81 or K-83 using a standard peptide coupling method, such as a DCC, mixed anhydride method, to give the compound designated as E-32, wherein R^G represents a heterocyclic ring. (The preparation of compounds K-81 and K-83 are described hereinafter in process 10).

(ii) Alternatively, the compound E-32 may be prepared by first converting the derivative E-29 to an acid chloride designated as E-30 and coupling the resulting acid chloride with compounds designated as K-81 or K-83 in a manner similar to that described in process 1-4.

(iii) Alternatively, a suitably substituted mono or polyhydroxy phenol derivative may be subjected to a Friedel-Crafts acylation with the acid chloride E-30 in a manner similar to that described in process 1-4 to

obtain yet another variant of compound E-32 in which R^G represents an aryl or aromatic heterocycle.

(iv) The variants of compound E-32 may be subjected to hydrogenolysis to obtain an amidine designated as E-33.

Process 5-2 for the preparation of variants of compounds E-32 and E-33 from the compound B-15:

The cyano group in compound B-15 may be converted to 1,2,4-oxadiazole by the method described in the above process 3-2. The resulting compound is then subjected to a standard deprotection procedure known in the art to remove the Z group to obtain a compound designated as E-31. The resulting compound E-31 may then be subjected to alkylation with F-46, G-53, H-62, H-63 (wherein R' is a leaving group, such as Cl, Br, I, OMes or OTs) and J-74, followed by in situ cyclization to obtain another variant of compound E-32. The resulting compound E-32 may be subjected to hydrogenation to obtain the amidine E-33.

Figure F

The preparations of variants of compound F-46 (used in the synthesis of key intermediates A-8 and B-20) via different synthetic routes are described below by the processes designated as process 6-1, 6-2 and 6-3, which are schematically presented in Figure F. The groups R^K, R^L and R^V in said compound F-46 represent substituents having the same meaning as the ring substituents in the definition of R^G. The group R represents $T(CH_2)_qCR^{23}R^{24}COR^{25}$; R' represents a H atom, a leaving group L, such as halogen, OMes or OTs, or a protected amino group, such as NHZ; Hal is the halogen F, Cl, Br or I and the remaining groups are as defined earlier.

Process 6-1 for the preparation of variants of compound F-46

(i) An appropriately substituted 1-(hydroxy-phenyl)ethanone may be treated with L $(CH_2)_qCR^{23}R^{24}COR^{25}$ to obtain a compound designated as F-46.

(ii) The compound F-46 thus obtained may then be treated with chlorosulfonic acid followed by treatment with a suitable amine $R^{21}R^{22}NH$ to get a variant of compound F-46 in which R^L and/or R^V is $SO_2NR^{21}R^{22}$, wherein R^L and R^V are as defined above.

(iii) The compound 1-(hydroxy-phenyl)-ethanone may be functionalised with a halogen through a standard nuclear halogenation method; preferably using N-halosuccinimide in solvents such as chloroform, dichloromethane, DMF, dioxane, THF, acetonitrile or acetic, or a mixture of at least two of these solvents, at from 0°C to reflux temperature to obtain compounds designated as F-39 and F-40, wherein R^L and R^V each represent a halogen, independently selected from, for example: Cl, Br and I.

(iv) The halogen substituted compounds F-39 and F-40 may be converted to ether or thio ether derivatives designated herein as F-41, wherein R^L/R^V are OR^{21} or SR^{21}, according to a reported procedure (Tetrahedron, 48, 3633, 1992; J. Org. Chem, 62, 5413, 1997 and R. Adams et. al. J. Amer. Chem. Soc., 81, 4927, 1959).

(v) The thio ether F-41 (R^L / R^V are SR^{21}), may be oxidized to the sulfoxide or sulfone designated as F-42 (R^L / R^V are $S(O)R^{21}$ or $S(O)_2R^{21}$) with a suitable oxidizing agent well known to those skilled in the art, preferably mCPBA, OXONE®, hydrogen peroxide or $NaIO_4$-Ru (IV).

(vi) The compounds F-39 to F-42 thus obtained may independently be alkylated with $L(CH_2)_qCR^{23}R^{24}COR^{25}$ (wherein the groups R^{23}, R^{24}, R^{25}

and the integer q are as defined earlier), using standard reaction conditions to obtain variants of compound F-46, wherein R is $O(CH_2)_qCR^{23}R^{24}COR^{25}$, R^K is H, and the remaining groups are as defined earlier.

Process 6-2 for the preparation of variants of compound F-46 in which the substituent R^V contains a nitrogen atom and is connected to the aromatic ring through N.

(i) An appropriately substituted 1-(hydroxy-phenyl)-ethanone is nitrated by a standard procedure known in the literature or a modification thereof, to give a compound designated as F-34, which may be treated with $L(CH_2)_qCR^{23}R^{24}COR^{25}$ to obtain a variant of the compound F-46, wherein R is $O(CH_2)_qCR^{23}R^{24}COR^{25}$; R^K is H; R^V is NO_2 ; and the remaining groups are as defined earlier.

(ii) The nitro group in compound F-34 may be subjected to reductive acylation using catalytic hydrogenation in the presence of an appropriate acid anhydride and a catalyst, such as Raney Ni, or a noble metal (such as Pd or Pt) based catalyst, to give a compound designated as F-43. F-43 may be subjected to alkylation with $L(CH_2)_qCR^{23}R^{24}COR^{25}$ to obtain a variant of the compound F-46, wherein R is $O(CH_2)_qCR^{23}R^{24}COR^{25}$; R^K and R^L are H; R^V is $NHCOR^{22}$; and the remaining groups are as defined earlier.

(iii) Alternatively, the OH group in compound F-34 may be protected with a suitable protecting group (Protecting groups in Org Synthesis, Ed, III, Green T.W. and Wuts. P. G. M, John Wiley & Sons Inc., p 246), such as a benzyl group, to obtain a compound designated as F-35. The compound F-35 may then be subjected to nitro group reduction using any conventional reduction method known in the art, for example, catalytic reduction using Raney Ni or $Zn\text{-}CoCl_2$ in DMF (Baruah. R. N. Ind. J.

Chem., 33B, 758, 1994) to obtain an amino compound designated as F-36. The amino compound F-36 may be treated with an appropriate acyl chloride ($R^{21}COCl$), sulfonyl chloride ($R^{21}SO_2Cl$), or chloroformate ($R^{21}OCOCl$) followed by deblocking of the benzyl group using any conventional method known in the art to obtain a compound designated as F-37 in which R^V is $NHCOR^{21}$, $NHSO_2NR^{21}R^{22}$, or $NHCOOR^2$, respectively. The compound F-37 may then be subjected to alkylation with $L(CH_2)_qCR^{23}R^{24}COR^{25}$ to obtain yet another variant F-46, wherein R is $O(CH_2)_qCR^{23}R^{24}COR^{25}$; R^V is $NHCOR^{21}$, $NHSO^2NR^{21}R^{22}$ or $NHCOOR^{21}$; R^K and R^L are H; and the remaining groups are as defined earlier.

Process 6-3 for the preparation of variants of compound F-46 from the compound F-38:

(i) An appropriate 1-(halo-phenyl)-ethanone designated as F-38 may be subjected to nucleophilic displacement utilizing $HS(CH_2)_qCR^{23}R^{24}COR^{25}$ either directly or through Cu(I)-thiolate using a suitable modification of a reported procedure (R. Adams et. al., J. Amer. Chem. Chem., 81, 4927, 1959) to obtain a variant of compound F-46, wherein R is $S(CH_2)_qCR^{23}R^{24}COR^{25}$; and the remaining groups are as defined earlier.

(ii) Alternatively, the compound F-38 may be subjected to a C-C bond forming reaction, preferably vinyl coupling with L-$CH=CH(CH_2)_qCR^{23}R^{24}COR^{25}$, wherein L is a halogen,and q is 0-5, using a Pd- or Ni- based catalyst to give compound F-46. F-46 may be hydrogenated to provide another variant of compound F-46, wherein R is $CH_2(CH_2)_qCR^{23}R^{24}COR^{25}$; q is 1-6; and the remaining groups are as defined earlier.

These variants of compound F-46 as prepared herein correspond to the compounds of the present invention of the general formula (I), preferably general

formulae (Ia) to (Ih), wherein T in $T\text{-}(CH_2)_qCR^{23}R^{24}COR^{25}$ (formula 5) represents CH_2 or S.

Process 6-4 for the preparation of variants of compound F-46 from compound F-44 or F-45

(i) An appropriately substituted di- or tri- hydroxy benzene may be subjected to a Friedel-Crafts acylation with an anhydride, such as $R'(CH_2)_nCR^DR^ECO)_2O$, or an acid chloride such as $R'(CH_2)CR^DR^ECOCl$, in the presence of a Lewis acid , such as $ZnCl_2$, $AlCl_3$. $HClO_4$, BF_3.etherate, $TiCl_4$, $FeCl_3$ or I_2, and in a solvent, such as $CHCl_3$, CH_2Cl_2, nitrobenzene or a C_6-C_{14} hydrocarbon, at a temperature ranging from an ambient temperature to 150°C, to obtain a compound designated as F-45. Alternatively, the appropriately substituted di- or tri- hydroxy benzene may be subjected to a Fries rearrangement with a phenol ester of the type $ArOCOCR^DR^E(CH_2)_nR'$ or a Houben-Hoesch acylation using a suitably substituted or unsubstituted nitrile $R'(CH_2)_nCR^DR^ECN$ according to a reported procedure (Junkichi Murai, Chem. Abstr. 50 981c, 1950) to obtain the compound F-45, wherein two or three of the groups R^1, R^K, R^L and R^V are OH and the remaining groups are as defined earlier.

(ii) The resulting compound F-45 may be subjected to alkylation with $L(CH_2)_qCR^{23}R^{24}COR^{25}$ to give the desired mono-, di- or tri- alkylated products representing another variant of compound F-46 wherein two or three of the groups selected from: R^1, R^K, R^L and R^V are $-O(CH_2)_qCR^{23}R^{24}COR^{25}$ and the remaining groups are as defined earlier.

(iii) In an alternative approach, the appropriately substituted polyhydroxy phenol may be alkylated first with $LCH_2CR^{23}R^{24}COR^{25}$ to obtain a compound designated as F-44, wherein two or three of the groups selected from: R, R^K, R^L and R^V are $-O(CH_2)_qCR^{23}R^{24}COR^{25}$, and

the remaining groups are as defined earlier. The intermediate F-44 may be subjected to a Friedel-Crafts acylation with $[R'(CH_2)_nCR^DR^ECO)_2O]$ or acid chloride $[R'(CH_2)CR^DR^ECOCl]$ in presence of a catalyst, such as $ZnCl_2$, I_2, $HClO_4$ or, most preferably, Zn powder (see Synth. Commun. 28, 2203, 1998) to obtain the desired variants of the compound F-46.

These variants of compound F-46 as prepared herein correspond to the compounds of the present invention of the general formula (I) or, more preferably, general formulae (Ia) to (Ih), in which the aromatic ring in R^G is substituted with at least two $T\text{-}(CH_2)CR^{23}R^{24}COR^{25}$ groups.

Figure G

The preparation of variants of compound G-53 (used in the synthesis of key compounds A-8, E-32 and B-20) via different synthetic routes is described below by the processes designated as process 7-1, which is schematically presented in Figure G. The groups R, R^K, R^L and R^V in said compound G-53 and the remaining groups are as defined earlier.

Process 7-1 for the preparation of compound G-53:

(i) Unsubstituted or substituted 1-(2,4-dihydroxyphenyl)ethanone may be subjected to various reactions similar to those described in the above process 6-1, such as halogenation of the compound 1-(2,4-dihydroxyphenyl)ethanone to obtain the mono-substituted compound designated as G-49 and the di- substituted compound G-50 (R^L/R^V = Cl/Br/I).

(ii) The compounds G-49 and G-50 may be converted into a ether or a thioether derivative where $R^L/R^V = OR^{21}/SR^{21}$ in a manner similar to that described in process 6-1 for the conversion of compounds F-39 and F-40 to the compound designated as F-41.

(iii) The thioether may be oxidized to a sulfoxide or sulfone where R^L/R^V is $S(=O)R^{21}$ or $S(=O)_2R^{21}$ with a suitable oxidizing agent.

(iv) The unsubstituted or appropriately substituted 1-(2,4-dihydroxy-phenyl) ethanone may be subjected to a Friedel-Crafts alkylation to obtain the compound designated as G-48, wherein R^K is OH.

(v) Friedel-Crafts acylation of G-47 (which is obtained by the reduction of 1-(2,4-dihydroxy-phenyl) ethanone by a standard procedure) or an appropriately substituted polyhydroxy phenol, such as substituted resorcinol or trihydroxy phenol, with a suitable anhydride, such as $R'(CH_2)_nCR^DR^ECO_2O$, or a suitable acid chloride, such as $R'(CH_2)_nCR^DR^ECOCl$, gives the compounds designated as G-48 and G-54. Alternatively, the compound G-47 or an appropriately substituted polyhydroxy phenol may be subjected to a Houben-Hoesch acylation with $R'(CH_2)_nCR^DR^ECN$ to give the compounds designated as G-48 or G-54, wherein R^K is OH and the remaining groups are as defined earlier.

(vi) The Claisen rearrangement of phenolic allyl ether G-56, wherein R^a, R^b, R^c, R^d and R^e are independently selected from: C_1-C_5 alkyl and C_7-C_{12} alkylaryl, resulted in G-57. The double bond reduction of G-57 according to a standard procedure well known in the art gives compound G-58, wherein its groups are as defined earlier.

(vii) The compounds G-54 and G-58 may be reduced partially or fully by a standard procedure to give the compound designated as G-55, wherein R^F is (H, OH) or (H, H) and the remaining symbols are as defined.

(viii) All the compounds G-48 to G-52, G-54, G-55, G-58 as well as 1-(2,4-dihydroxy-phenyl)ethanone, are treated with $L\text{-}(CH_2)_qCR^{23}R^{24}COR^{25}$ using a standard procedure to give a variant of compound G-53, wherein

R^K is OH; one or more of the groups R, R^L and R^V represent $O(CH_2)_qCR^{23}R^{24}COR^{25}$; and the remaining groups are as defined earlier.

(ix) The compounds G-53 in which R^K is OH, may be further subjected to substitution reactions using an appropriate alkyl halide, acyl halide, sulfonyl chloride or chloroformate, to obtain variants of compound G-53, wherein R^K is $OCOR^{21}$, $OS(=O)_2R^{21}$ or $-OCOOR^{21}$; one or more of the groups R, R^L and R^V are $O(CH_2)_qCR^{23}R^{24}COR^{25}$; and the remaining symbols are as defined earlier.

Figure H

The preparation of variants of compounds H-63, H-71 and H-72, wherein R^K and/or $R^U$are/is OH or substituted OH (used in the synthesis of key intermediates A-8, B-20 and E-32) via different synthetic routes is described below in the processes designated as 8-1 and 8-2, which are schematically presented in Figure H.

Process 8-1 for the preparation of compound H-63 and its variants:

(i) An appropriately substituted dihydroxy benzaldehyde, such as 3,4-dihydroxy benzaldehyde, may be subjected to a sequence of reaction steps such as alkylation with $L\text{-}(CH_2)_qCR^{23}R^{24}COR^{25}$ to obtain the compound designated as H-59, wherein R is $O(CH_2)_qR^{23}R^{24}COR^{25}$. The compound H-59 may then be subjected to a Baeyer-Villiger oxidation (I. M. Godfrey *et. al*, J.C.S. Perkin I, 1353, 1974) followed by hydrolysis of the resulting formyl ester and subsequent alkylation of phenolic OH to obtain the compound designated as H-60, wherein R^a, R^b and R^c are independently selected from: C_1-C_5 alkyl and C_7-C_{12} alkyl aryl.

(ii) The compound H-60 may be subjected to a Friedel-Crafts acylation (H. M. Meshram. *et. al.*, Synth. Commun, 28, 2203, 1998) with $R'(CH_2)_nCR^DR^ECOCl$ in the presence of a Lewis acid catalyst, such as Zn, BF_3.etherate, $FeCl_3$, $AlCl_3$ and $ZnCl_3$, preferably Zn, in the presence of at least one organic solvent selected from, for example: toluene, benzene, heptane, kerpsene, CS_2, CCl_4, and nitrobenzene, preferably toluene, and in situ cleavage of the allyl group to obtain the desired compound H-63, wherein R and R^V are $O(CH_2)_qCR^{23}R^{24}COR^{25}$; R^K is OH; R^L is H; R^F is O; and the remaining groups are as defined earlier.

(iii) A variant of compound H-63 (wherein R^K represent OR^{21}, $OCOR^{21}$, $OS(=O)_2R^{21}$or $OCOOR^{21}$, and the remaining groups are as defined earlier) may be obtained by treatment of the compound H-63, wherein R^K is OH, with an appropriate alkyl halide, acyl halide, sulfonyl halide or chloroformate under standard reaction conditions well known in the art.

(iv) Yet another variant of compound H-63, wherein R and R^V represent $O(CH_2)_qCR^{23}R^{24}COR^{25}$; R^F is (H, H); R^D and R^E are H; and the remaining groups are as defined earlier, may be prepared by subjecting the compound H-59 to a Wittig reaction to obtain the compound designated as H-64 which on hydrogenation gives the desired variant.

(v) An appropriately substituted 1-(2,5-dihydroxy-phenyl)-ethanone may be alkylated with $L\text{-}(CH_2)_qCR^{23}R^{24}COR^{25}$ to give a variant of compound H-63 (wherein R is H ; R^V is $O(CH_2)_qCR^{23}R^{24}COR^{25}$; R^F is O; and the remaining groups are as defined earlier).

(vi) Another variant of compound H-63 may be obtained by subjecting the compound H-60 to a Friedel-Crafts alkylation with $R'(CH_2)_nCR^DR^ECH_2L$, wherein R' is H, NHZ or L and L is a leaving group, such as halogen. OMes or OTs, to obtain the compound designated as H-61, followed by the removal of the allyl group from the resulting

compound H-61 to obtain another variant of compound H-63, wherein R^F represents (H, H); R and R^V are $O(CH_2)_qCR^{23}R^{24}COR^{25}$; R^K is OH; and the remaining groups are as defined earlier.

(vii) Yet another variant of compound H-63 may be obtained by reducing the carbonyl group in compound H-63 (wherein R^F is O) by a standard procedure known in the art to give compound H-63, wherein R^F represents (H, OH) or (H, H), and the remaining groups are as defined earlier.

(viii) The allyl group in compound H-61 may be removed by a standard method to give the compound designated as H-62, wherein R^F is (H, H). The compound H-62 may be subjected to a substitution reaction with an appropriate alkyl halide, acyl halide or chloroformate leading to the formation of a variant of the compound H-63, wherein R^F is (H, H); R^K represents OR^{21}; $OCOR^{21}$; $OCOR^{21}$; $OS(=O)_2R^{21}$ or $OCOOR^{21}$; and the remaining groups are as defined earlier.

Process 8-2 for the preparation of variants of compound H-71 and H-72 (wherein R^K and/or R^U are/is OH or substituted OH):

(i) Phloroglucinol may be subjected to O-alkylation (Chem. Abstr., 50, 977d, 1956) to obtain 5-methoxy-1,3-benzenediol, designated as H-65.

(ii) Alternatively, phlororoglucinol may be converted to 5-benzyloxy-1,3-benzenediol designated as H-68 by following a sequence of reactions according to a reported procedure (Haruo. Kawamoto. *et. al.* ,Synth. Commun. 26, 531, 1996).

(iii) The compounds H-65 and H-68 thus obtained may be subjected to a novel modification of the Houben-Hoesch reaction in which a suitably

protected amino nitrile of the type $R'(CH_2)_nCR^DR^ECN$, wherein R' is H, NHZ or L, and L is a leaving group, such as halogen, OMes or OTs, may be treated with dry HCl in presence of a Lewis acid, such as $ZnCl_2$ or BF_3.etherate, in a solvent, such as ether, THF or dioxane, followed by hydrolysis of the resulting imine hydrochloride to obtain the compound designated as H-69, wherein its groups are as defined earlier.

(iv) The compound H-69 may be subjected to selective alkylation with $L-(CH_2)_qCR^{23}R^{24}COR^{25}$, wherein L is a leaving group, such as halogen, OMe–s or OTs, to give the compound designated as H-70, wherein R is $O(CH_2)_qCR^{23}R^{24}COR^{25}$, and the remaining groups are as defined earlier.

(v) The compound H-70 may be subjected to further reactions such as O-alkylation, O-sulphonation, O-acylation or carbonate formation reaction as described earlier resulting in variants of the compound H-70 designated as H-71, wherein R^U represents OR^{21}, $OCOR^{21}$, $OS(=O)_2R^{21}$ or $OCOOR^{21}$; and the remaining groups are as defined earlier.

(vi) The compound H-71 in which R' is NHZ and optionally R^K is OCH_2Ph may be subjected to a standard deblocking reaction known in the art, to obtain an the amino compound designated as H-72, wherein B is halogen, acetate or formate.

Figure J

The preparation of compounds J-74 and J-77 (used in the synthesis of key intermediates A-8, B-20 and E-32) via different synthetic routes is described below by the processes designated as process 9-1, which is schematically presented in Figure J. In the compounds referred to below, the groups R', R^F, R^D, R^E, and n are as described earlier. R is $T(CH_2)_qCR^{23}R^{24}COR^{25}$ or OCH_2Phenyl and R^K, R^L, R^U and R^V are independently selected from the substituent groups provided in the definition of R^G.

Process 9-1 for the preparation of compounds J-74 and J-77

(i) Appropriately substituted compounds F-46, G-53, H-63, H-70 and H-71 (in all these compounds n is 0, $R^{'} = R^{D} = R^{E} = H$) (prepared by processes described hereinabove) may be subjected to a standard α-bromination reaction, most preferably by using bromine in an appropriate solvent, for example, an organic solvent such as, optionally in the presence of a catalyst, such as $AlCl_3$ or other Lewis acid, to obtain the mono-bromo compound designated as J-74. Alternatively, the bromination may be carried out using $CuBr_2$ according to a known precedure (L C. King. et. al., J. Org. Chem., 29, 3459, 1964), leading to the formation of the mono bromo compound J-74.

(ii) The mono-bromo derivative J-74 may then be converted to a hexamine salt according to a reported procedure (L.M. Long. *et al* J. Amer. Chem. Soc., 71, 2473, 1949) which may in turn be subjected to a cleavage reaction using an aqueous acid optionally in presence of a lower alcohol, such as MeOH, EtOH, or iPrOH, to obtain the amine hydrochloride designated as J-77, and a small amount of acid (R^{25} is OH) as a side product, wherein R^{F} is O; R^{D} and R^{E} are H; n is 0; and the remaining groups are as described.

(iii) The compound J-77, if required, may be purified by treating the mixture of the compound and the residual acid with a suitable reagent, such as $(Boc)_2O$, for protecting the amino group in an alkaline condition to obtain the separated compounds designated as J-75 (wherein R^{F} is O; R^{D} and R^{E} are H; n is 0) and J-76, (wherein R^{F} is O; R^{D} and R^{E} are H; n is 0; and R and/or R^{V} = $T(CH_2)_qCR^{23}R^{24}COOH$). Deprotection of the compound J-75 may be carried out using a standard deprotecting reagent known in the art of peptide synthesis to obtain the desired compound J-77.

(iv) Likewise, the other compound J-76 (wherein R^{25} is OH) may be converted to its corresponding ester by treatment with R^5OH or R^5SH, in the presence of DCC and DMAP according to a reported procedure(Alfred. Hassner. *et. al.* Tetrahedron Lett. 4475, 1978) to obtain a variant of the compound J-75, wherein R is $O(CH_2)_qCR^{23}R^{24}COR^{25}$, and R^{25} is OH.

(v) Alternatively, the compound J-76 in which R^{25} is OH may be converted to an amide by treatment with an appropriate amine of formula R^5R^6NH in which R^5 and R^6 are as defined , using a standard peptide coupling procedure resulting in a variant of the compound J-75.

(vi) Deprotection of the Boc group of the compound J-75 may be carried out using formic acid, TFA or HCl in an organic solvent in presence of anisole or thioanisole to give the compound J-77, wherein R^F is O; R^D and R^E are H; n is 0; and the remaining groups are as defined earlier.

(vii) Alternatively, the compounds F-46, G-53, H-63, H-70 and H-71 [wherein R' is L and R^F is O or (H, H)] may be converted to a hexamine salt (see L.M. Long. *et al* J. Amer. Chem. Soc., 71, 2473, 1949), which may be subjected to cleavage using aqueous acid, optionally in presence of a lower alcohol, such as MeOH, EtOH or iPrOH, to obtain the corresponding amine hydrochloride J-77. Purification of said amine hydrochloride, if required, may be carried out by treating the mixture of compound J-77 and acid with a suitable reagent such as $(Boc)_2O$ for protecting the amino group in an alkaline condition to obtain the compound J-73, wherein R^F is O or (H, H); and the remaining groups are as defined earlier.

(viii) Deprotection of the compound J-73 may be carried out using a standard deprotecting reagent known in the art of peptide synthesis to

obtain the compound J-77, wherein R^F is O or (H, H) and the remaining groups are as defined earlier.

(ix) Further, if required, functional group modification such as alkylation, acylation, sulphonation or carbonate formation may be carried out on the OH, SH and/or NHR^{21} group(s) of the compound J-75, wherein one or more of the groups R^K, R^L, $R^U$and R^V independently represent OH, SH or NHR^{21} to obtain the desired variant of the compound, wherein one or more of the groups R^K, R^L, R^U and R^V independently represent OR^{21}, SR^{21} or $NR^{21}R^{22}$.

a. The thus obtained intermediate J-75 may be subjected to deprotection of the Boc group leading to the formation of the variant of compound J-77, wherein all its groups are as defined earlier.

(xi) Variants of the compound J-75, wherein one or more of the groups R^K, R^L R^V and R^U represent SR^{21}, may be subjected to functional group modification, such as oxidation of the thiol ether to give a variant of compound J-75, wherein one or more of the groups R^K, R^L R^V and R^U represent $S(=O)R^{21}$ or $S(=O)_2R^{21}$, which may further be subjected to Boc deblocking leading to the formation of variant J-77, wherein all its groups are as defined earlier.

(xii) Variants of the compound J-75, wherein one or more of the groups R^K, R^L R^V and R^U represent NO_2, may be subjected to reduction to obtain the corresponding amine, which may further be treated with an appropriate acyl halide, sulfonyl halide or chloroformate to give a variant of compound J-75, wherein one or more of the groups R^K, R^L R^V and R^U represent $NHCOR^{21}$, $NHSO_2R^{21}$ or $NHCOOR^{21}$, which in turn may be subjected to removal of the Boc group leading to the formation of variant compound J-77, wherein all its groups are as defined earlier.

(xiii) Yet another approach for the preparation of a variant of the compound J-77, wherein R^F is O; R^D and R^E are H; n is 0; R is OCH_2Ph; and the remaining symbols are as defined earlier, may involve the preparation of a compound designated as J-78 from an appropriately substituted 1-(hydroxy-phenyl) ethanone through phenolic OH group protection (preferably by a benzyl group) followed by the similar sequence described earlier. After deprotection of the benzyl group, the phenolic OH group may be alkylated with $L\text{-}(CH_2)_qCR^{23}R^{24}COR^{25}$ to obtain the compound J-75. Finally, both compounds J-75 and J-78 may be subjected to removal of the Boc group to obtain variants of the compound J-77. The compound J-77 in which R is OCH_2Ph is used in the synthesis of fragment B-20.

Figure K

The preparation of compounds K-81, K-83, and K-84 (used in the synthesis of key intermediates A-8 and E-32) via different synthetic routes is described below by the process designated as process 10-1, which is schematically presented in Figure K. The groups n, R^D, R^E, q and T in said compounds have the same meaning as described for the general formulae (I) and (Ia) to (Ih) and Q represents CH or N.

Process 10-1 for the preparation of compounds K-81, K-83 and K-84:

(i) N-Protected 4-hydroxy piperidine may be treated with $L(CH_2)_qCR^{23}R^{24}COR^{25}$ in which L and q are as defined earlier, to obtain a compound designated as K-79, wherein T is O.

(ii) The hydroxy group of the N-protected 4-hydroxy piperidine may be converted into a suitable leaving group, such as OMes or OTs , followed by treatment with an amine of the type $H_2N(CH_2)_qCR^{23}R^{24}COR^{25}$ or a thiol

of the type $HS(CH_2)_qCR^{23}R^{24}COR^{25}$ to give a variant of compound K-79, wherein T is NH or S.

(iii) Another variant of the compound K-79, wherein T is $-CH_2-$, may be obtained by catalytic hydrogenation of the corresponding pyridine derivative, preferably using PtO_2 in acetic acid, to obtain an amine followed by protection of the resulting amine with a suitable protecting group such as Boc or Z.

(iv) Alternatively, isonicotinic acid may be reduced to isonipecotic acid according to a reported procedure (US-A 7,399, 68), which after N-protection with a suitable protecting group, preferably Z or Boc, may be converted to an aldehyde designated as K-80 according to a reported procedure (M. S. Egbertson et al, J. Med. Chem, 37, 2537, 1994). The aldehyde may then be treated with an appropriate Wittig reagent to obtain a variant of compound K-79, wherein $T(CH_2)_q$ represents $-CH=CH(CH_2)_{q-1}$. The double bond may be subjected to any conventional reduction method known in the art, preferably hydrogenation resulting in a variant of compound K-79, wherein T is $-CH_2-$.

(v) The removal of the Z or Boc group may be carried out using a standard procedure known in the art to obtain a compound designated as K-81, wherein all its groups are as defined earlier.

(vi) Commercially available piperazine or its derivatives may be converted to a compound designated as K-83, in a similar manner as described above in this process. A final deprotection step to remove the Boc or Z group with an appropriate deprotecting reagent known in the art provides the amino compound K-83.

(vii) Compounds K-83 and K-81 may be coupled with a suitably protected amino acid, such as Z- or Boc- $NH(CH_2)_nCR^DR^ECOOH$ (wherein the symbols are as defined earlier), using a standard peptide coupling method, preferably DCC-HOBt or IBCF-NMM, to obtain the compound designated as K-82, which may be further subjected to a standard Boc or Z deprotection to obtain the compound K-84, wherein Q is CH or N; and the remaining groups are as defined earlier.

The compounds K-81, K-83, and K-84 obtained by the above process are required for the preparation of compounds of general formula (I), preferably of general formulae (Ia) to (Ih), in which R^G represents substituted piperidine and substituted piperazine.

Compounds according to the general formula (I) or general formulae (Ia) to (Ih) can be used to antagonize the activity of GP IIb/IIIa receptors and are beneficial pharmaceutical compounds for the treatment of various thrombotic diseases. In the context of the present invention, compounds of this invention may be administered to patients, where prevention of thrombosis by inhibiting the binding of fibrinogen to the platelet membrane glycoprotein complex GPIIb/IIIa receptor is desired. This would include patients with cardiovascular (arterial and/or venous) and cerebrovascular thromboembolic diseases, under which the following can be included (though are not limited to):

1. arterial thromboembolism
2. cerebral thromboembololism
3. cerebral arterial thrombosis
4. coronary thrombosis
5. deep vein thrombosis
6. diabetes-related thromboembolic disorders

7. sudden ischemic emergencies

8. myocardial infarction

9. pulmonary thromboembolisms

10. stroke

11. thrombophlebitis

12. transient ischemic attack

13. unstable angina and venous thrombosis

14. kidney thromboembolism

These compounds are useful during surgery on peripheral arteries (arterial grafts, carotid endarterectomy) and cardiovascular surgery where manipulation of arteries and organs, and/or the interaction of platelets with artificial surfaces, such as surgical instruments and the heart-lung machine leads to platelet aggregation. The aggregated platelets may form thrombi and thromboemboli. Compounds of this invention may be administered to these surgical patients to prevent such complications. (S. D. Berkowitz, American Heart Journal, 2001, 142, 7 - 13).

Extracorporeal circulation is routinely used for cardiovascular surgery in order to oxygenate blood. Platelets adhere to surfaces of the extracorporeal circuit. Adhesion is dependent on the interaction between GP IIb/IIIa receptors on the platelet membranes and fibrinogen adsorbed to the surface of the circuit (Gluszko et al., Am. J. Physiol., 1987, 252(H), 615-621,). Platelets released from an artificial surface show impaired hemostatic function. Compounds of this invention may be administered to prevent this adhesion.

Other applications of these compounds include (though are not limited to):

1. prevention of platelet thrombosis

2. thromboembolism and reocclusion during and after thrombolytic therapy and prevention of platelet thrombosis

3. thromboembolism and reocclusion after angioplasty or coronary artery bypass surgery

4. prevention of myocardial infarction

5. prevention of blood clots after orthopedic surgery

Cell adhesion (cell-cell or cell-matrix) involves processes that require proteins like fibrinogen, fibronectin, vitronectin and vWF. These proteins bind to the integrin superfamily of receptors to produce their action. Thus, GP IIb/IIIa antagonists which antagonize the integrin superfamily of receptors may be useful in diseases, other than the above, which involve cell adhesion processes. Such diseases include (though are not limited to):

1. adult respiratory distress syndrome

2. allergies

3. asthma

4. rupture of atherosclerotic plaques

5. autoimmune diseases

6. inflammation, bone degradation

7. contact dermatitis

8. diabetic retinopathy

9. eczema

10. graft versus host disease

11. inflammatory bowel disease

12. metastasis

13. organ transplantation rejection

14. osteoarthritis

15. osteoporosis

16. psoriasis

17. rheumatoid arthritis

18. septic shock

19. tumors

The present invention therefore also relates to the compounds of the general formula (I) or general formulae (Ia) to (Ih) and/or their pharmaceutically acceptable salts and/or their pro-drugs for use as pharmaceuticals (or medicaments), to the use of the compounds of the general formula (I) or general formulae (Ia) to (Ih) and/or their physiologically tolerable salts and/or their pro-drugs for the manufacture of medicaments for the production of pharmaceuticals for the inhibition of GP IIb/IIIa receptors or for the therapy or prophylaxis of the diseases and conditions mentioned above, for example for the production of pharmaceuticals for the therapy and prophylaxis of cardiovascular (arterial and/or venous) and cerebrovascular thromboembolic diseases, etc., and to methods of treatment aiming at such purposes including methods for said therapies and prophylaxes. The present invention furthermore relates to pharmaceutical compositions that contain an effective amount of at least one compound of the general formula (I) or general formulae (Ia) to (Ih) and/or its physiologically tolerable salts and/or its prodrugs in addition to a customary pharmaceutically acceptable carrier, and to a process for the production of a pharmaceutical,

which comprises bringing at least one compound of general formula (I) or general formulae (Ia) to (Ih) into a suitable administration form using a pharmaceutically suitable and physiologically tolerable excipient and, if appropriate, further suitable active compounds, additives or auxiliaries. The pharmaceutical preparation comprises the compound of general formula (I) or general formulae (Ia) to (Ih) in an amount adequate to antagonize GP IIb/IIIa receptors. The present invention also relates to a method for the preparation of a medicament for the treatment or prevention of disorders associated with activation of GP IIb/IIIa receptors, characterized in that at least one compound of the general formula (I) or general formulae (Ia) to (Ih) is used as the pharmaceutically active substance.

The pharmaceuticals can be administered orally, for example in the form of pills, tablets, coated tablets, capsules, granules or elixirs. Administration, however, can also be carried out rectally, for example in the form of suppositories, or parentally, for example intravenously, intramuscularly or subcutaneously, in the form of injectable sterile solutions or suspensions, or topically, for example in the form of solutions or transdermal patches, or in other ways, for example in the form of aerosols or nasal sprays.

The pharmaceutical preparations according to the invention are prepared in a manner known per se and familiar to one skilled in the art. Pharmaceutically acceptable inert inorganic and/or organic carriers and/or additives can be used in addition to the compound(s) of the general formula (I) or general formulae (Ia) to (Ih) and/or its (their) physiologically tolerable salts and/or its (their) prodrugs. For the production of pills, tablets, coated tablets and hard gelatin capsules it is possible to use, for example, lactose, corn starch or derivatives thereof, gum arabic, magnesia or glucose, etc. Carriers for soft gelatin capsules and suppositories are, for example, fats, waxes, natural or hardened oils, etc. Suitable carriers for the production of solutions, for example injection solutions, or of emulsions or syrups are, for example, water, physiological sodium chloride solution or alcohols, for example, ethanol, propanol or glycerol, sugar solutions,

such as glucose solutions or mannitol solutions, or a mixture of the various solvents which have been mentioned.

The pharmaceutical preparations normally contain about 1 to 99 %, preferably about 5 to 70%, most preferably from about 10 to about 30 % by weight of the compounds of the general formula (I) or general formulae (Ia) to (Ih) and/or their physiologically tolerable salts and/or their prodrugs. The amount of the active ingredient of the general formula (I) or general formulae (Ia) to (Ih) and/or its physiologically tolerable salts and/or its prodrugs in the oral pharmaceutical preparations normally is from about 5 to 200 mg. The dose of the compounds of this invention, which is to be administered, can cover a wide range. The dose to be administered orally daily is to be selected to suit the desired effect. About 10 to 100 mg are preferably administered orally daily per patient. If required, higher or lower daily doses can also be administered. For intravenous administration the most preferred dose will range from about 0.01 to 3 mg per patient. Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient that is effective in achieving the desired therapeutic response for a particular patient, composition and mode of administration without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and /or materials used in combination with the particular compounds employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

In addition to the active ingredients of the general formula (I) or general formulae (Ia) to (Ih) and/or their physiologically acceptable salts and/or prodrugs and to

carrier substances, the pharmaceutical preparations can contain additives such as, for example, fillers, antioxidants, dispersants, emulsifiers, defoamers, flavor corrigants, preservatives, solubilizers or colorants. They can also contain two or more compounds of the general formula (I) or general formulae (Ia) to (Ih) and/or their physiologically tolerable salts and/or their prodrugs. Furthermore, in addition to at least one compound of the general formula (I) or general formulae (Ia) to (Ih) and/or its physiologically tolerable salts and/or its prodrugs, the pharmaceutical preparations can also contain one or more other therapeutically or prophylactically active ingredients.

The compounds of the present invention may be used as drugs in the treatment of thrombotic diseases either alone or as part of combined therapies. For instance, the compounds of the present invention may be used in combination with known antithrombotic agents. If formulated as a fixed dose, such combination products employ the compounds of the present invention within the dosage range described above and the other pharmaceutically active agent within its approved dosage range. For example, in the 2nd SYMPHONY trial patients were treated with sibrafiban and aspirin. In the NICE-4 trial, a combination of abciximab and enoxaparin was studied (Bhatt, D. L. and Topol, E. J., JAMA, 2000, 284,1549 - 1558).

It is understood that modifications that do not substantially affect the activity of the various embodiments of this invention are included within the invention disclosed herein. Accordingly, the following examples are intended to illustrate but not to limit the present invention.

The examples as described below are given by way of illustration only and are not to be construed as limiting the invention in any way in as much as many variations of the invention are possible within the meaning of the invention.

Example 1:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid methyl ester, acetic acid salt

A solution of the compound of example 1i (1.49g; 2.76 mmol) in MeOH (40 ml) was treated with ammonium acetate (0.86g; 11mmol), refluxed for 1h, concentrated, purified using flash chromatography (RP-18 column, MeOH:0.2 % AcOH in water/1:1) and crystallized using dry MeOH-ether to obtain the title compound. Yield, 0.08g (6.6%); mp,181-182°C; MS (ESI): 404 (M^++Na^+), 382 (M^++1); analysis: $C_{22}H_{23}N_3O_7$,0.5 H_2O requires, C, 58.66; H, 5.55; N, 9.33; found: C, 58.31; H, 5.23; N, 9.72%.

Example 1a:

2-Methyl-4-nitro-benzoic acid ethyl ester

Thionyl chloride (48 ml) was added slowly to 2-methyl-4-nitro-benzoic acid (85g; 0.469 mol) and the reaction mixture was refluxed (4-6h) to give a clear solution. It was brought to room temperature then chilled to 0°C. Dry alcohol (150 ml) was added slowly with vigorous stirring and the reaction mixture was refluxed for 30 min. It was concentrated, treated with crushed ice, $NaHCO_3$ and extracted with EtOAc. The EtOAc layer was washed with water, brine, dried (Na_2SO_4), concentrated, purified using flash chromatography (silica gel, 10% EtOAc- PE 60-80°C) and crystallized using EtOAc- PE 60-80°C to obtain the title compound as light yellow crystals. Yield, 83.8 g (85.4%); mp, 68-71°C; IR: 2950, 1720, 1525; MS (EI): 209(M^+), 192. 181, 163 (100%), 89.

Example 1b:

4-Amino-2-methyl-benzoic acid ethyl ester

Compound of example 1a (41g; 196 mmol) in MeOH (500 ml) was hydrogenated using Raney Ni (2g) at 50 psi for 2h. The solution was filtered free off the catalyst, concentrated and purified using flash chromatography (silica gel, 10% EtOAc- PE 60-80°C, 30% EtOAc- PE 60-80°C) to obtain the title compound. Yield, 33g (93.94%); mp, 77-80°C, MS (EI): 179 (M^+), 134 (100%), 106, 77; analysis: $C_{10}H_{13}NO_2$ requires, C, 67.02; H, 7.31; N, 7.82; found, C, 67.25; H, 7.26; N, 7.57%.

Example 1c:

4-Cyano-2-methyl-benzoic acid ethyl ester

Compound of example 1b (32g; 178 mmol) was treated with conc. HCl (64 ml) and water (320 ml), cooled to 0°C, then treated to a dropwise addition of an aqueous solution of $NaNO_2$ (12.33g; 178 mmol, 320 ml) over a period of 1h at 0-5°C. The diazonium salt solution was neutralized with Na_2CO_3 and added slowly to an aqueous solution of KCN and CuCN (13.38g; 204.4 mmol, 19.34g; 204.4 mmol, 500 ml), maintained at 0-5°C, with vigorous stirring over a period of 1h. The reaction mixture was stirred for 30 min. at 0-5°C and left stirring overnight at room temperature. It was subsequently heated on steam bath for 30 min., treated with an aqueous 10% $FeCl_3$ solution and extracted with EtOAc (3x500 ml). The organic layer was washed with water, brine, dried (Na_2SO_4), concentrated, purified using flash chromatography (silica gel, 5% EtOAc- PE 60-80°C) and crystallized using EtOAc- PE 60-80°C to obtain the title compound as a pure white solid. Yield, 20g (59.2%); mp, 64-65°C; MS (EI): 189 (M^+), 144 (100%), 116, 89; analysis: $C_{11}H_{11}NO_2$, 0.5 H_2O requires C, 66.70; H, 6.06; N, 7.07; found: C, 67.11; H, 5.88; N, 6.88%.

Example 1d:

2-Bromomethyl-4-cyano-benzoic acid ethyl ester

NBS (22.8g; 128 mmol) was added to a solution of the compound of example 1c (22g; 116.4 mmol) in CCl_4 (1 lit.), followed by a catalytic amount of AIBN (~ 10 mg). The reaction mixture was refluxed (6-7 h), cooled to room temperature, washed with water, brine, dried (Na_2SO_4), concentrated, purified using flash chromatography (5% EtOAc-PE 60-80°C) and crystallized using EtOAc- PE 60-80°C to obtain the title compound. Yield, 15.8g (50.64%); mp, 70-72°C; analysis: $C_{11}H_{10}BrNO_2$, 0.5 H_2O requires C, 49.25; H, 3.73; N, 5.22; found: C, 49.27; H, 3.62; N, 4.79%.

Example 1e:

(4-{2-Amino-acetyl}-phenoxy)-acetic acid methyl ester, hydrochloride

Example 1f:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-phenoxy)-acetic acid

Hexamine (7.56g; 54 mmol) was added with stirring to a solution of (4-{2-Bromo-acetyl}-phenoxy)-acetic acid methyl ester (15g; 52.3 mmol) in dry chloroform (300 ml) and the reaction mixture was stirred overnight. Dry ether (250 ml) was added and the white solid that separated was filtered, washed with $CHCl_3$-Ether 1:1 (2x30 ml), dried (22 g), treated with MeOH (35 ml), conc.HCl (17.5 ml) and stirred overnight at room temperature. The reaction mixture was concentrated, filtered and the solid obtained was washed with cold water (5 ml), ether, ethyl acetate and dried to obtain the title compound of example 1e (5.2g, 39%). The filtrate was diluted with water (100 ml) and neutralised with $NaHCO_3$ at 0°C. A solution of $(Boc)_2O$ (8.7g) in dioxane (100 ml) was added and the mixture was stirred for 2h, concentrated and extracted with EtOAc. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated to obtain the crude product which was hydrolysed with 1N methanolic NaOH for 1h. The reaction mixture was processed as is routinely done and crystallised using EtOAc-PE 60-80°C to obtain the title compound of example 1f (8.1g, 50%); mp, 51-53°C; MS (ESI^+): 332 (M^++Na^+) 310 (M^++1), (ESI^-) 308 (M^+-1).

Example1g:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid methyl ester

$NaHCO_3$ (4.6g; 54.8 mmol) was added with stirring to a solution of the compound of example 1e (5g; 16.44 mmol) in dry DMF (50 ml) at –25°C. Subsequently compound of example 1d (3.673g; 13.7 mmol) in dichloromethane (50 ml) was added drop wise over a period of 1h. The reaction mixture was maintained at –25°C for an additional 30 min., gradually brought to room temperature and stirred overnight. It was diluted with water and extracted with EtOAc (3x30 ml). The organic layer was washed with water, dilute aqueous HCl, brine, dried (Na_2SO_4), concentrated and purified using flash chromatography (silica gel, 5-10 % CH_3CN in $CHCl_3$) to obtain the title compound. Yield, 1.5g (30.12%); mp. 185-187°C; MS (EI): 364 (M^+), 193 (100%), 171, 116; analysis: $C_{2C}H_{16}N_2O_5$ requires, C, 65.93; H, 4.43; N, 7.69; found, C, 65.64: H, 4.44; N, 7.22%.

Example 1h:

(4-{2-[1-Oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy) acetic acid methyl ester

H_2S gas was passed through a solution of the compound of example 1g (0.6g, 1.65 mmol) in pyridine/ Et_3N :: 5/1(50 ml) for 30 min. to obtain an amber coloured solution which was stirred at room temperature till the starting material was consumed. It was concentrated and purified using flash chromatography (silica gel, 3% MeOH in $CHCl_3$) to obtain the title compound as a pale yellow solid. Yield, 0.628g (95.73%); ^{1}H-NMR (DMSO-D_6): 3.72 (3H, s, $OC\underline{H}_3$), 4.56, 4.98, 5.13 (6H, 3xs, 3x$C\underline{H}_2$), 7.12 (2H, d, J=8:7, H-2′ & H-5′), 7.75 (1H, d, J=7.75, H-7), 7.96 (1H, dd, J=7.75, 2.0, H-6), 8.10 (1H, d, J=2.0, H-4), 8.05 (2H, d, J=8.72, H-3′ & H-5′), 9.70, 10.10 (2H, 2xs, $N\underline{H}_2$).

Example 1i:

(4-{2-[5-Methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid methyl ester, hydro iodide

A solution of the compound of example 1h (0.628g; 15.78 mmol) and iodomethane (1 ml) in dry acetone (45 ml) was refluxed for 3h. It was concentrated to obtain the title compound as a yellow solid. Yield, 0.8g (93.89%); ^{1}H-NMR (DMSO-D_6): 2.84 (3H, s, $SC\underline{H}_3$), 3.72 (3H, s, $OC\underline{H}_3$), 4.64, 4.98. 5.17 (6H, 3xs, 3x$C\underline{H}_2$), 7.12 (2H, d, J=9.15, H-2′ & H-6′), 7.98 (2H, m, H-6 & H-7), 8.04 (2H, d, J=9.15, H-3′ & H-5′), 8.15 (1H, br, H-4).

Example 2:

(4-{2-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)–acetic acid methyl ester, hemihydrate

A mixture of the compound of example 1g (0.3g; 0.824 mmol), hydroxylamine hydrochloride (0.22g; 3.3 mmol) and $NaHCO_3$ (0.3g; 3.3 mmol) in MeOH (25 ml) was stirred at room temperature for 3h. It was concentrated, purified using flash chromatography (silica gel, 5-10 % MeOH +1% AcOH in $CHCl_3$) and crystallized from MeOH-ether to obtain the title compound. Yield,

0.135g (40.3%); mp, 175-176°C; analysis: $C_{20}H_{19}N_3O_6$, 0.5 H_2O requires, C, 59.19; H, 4.96; N, 10.33; found: C, 58.32; H, 4.72; N, 10.12%.

Example 3:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy) - acetic acid ethyl ester

The title compound was obtained from the compound of example 3d using the procedure described in Example 1. The crude product was purified using flash chromatography (RP-18, MeOH: 0.2% AcOH (1:1)) and crystallized from dry MeOH-ether. Yield, 44%; mp, 185-87°C; MS (ESI^+): 396 (M^++1); analysis: $C_{23}H_{25}N_3O_7$ requires: C, 60.65; H, 5.53; N, 9.23; found: C, 60.27; H, 5.49; N, 9.20%.

Example 3a:

(4-{2-Amino-acetyl}-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from (4-{2-Bromo-acetyl}-phenoxy)-acetic acid ethyl ester (9.03g; 30 mmol) using the procedure described in example1e and example 1f. Yield, 2.9g (35.5%); ^{1}H-NMR ($CDCl_3$): 1.33 (3H, t, J=7.3, $CH_2\underline{CH_3}$), 4.30 (2H, q, J=7.3, $\underline{CH_2}CH_3$), 4.60, 4.83 (4H, 2xs, 2x$\underline{CH_2}$), 7.15 (2H, d, J=8.7, H-3 & H-5), 8.08 (2H, d, J=8.7, H-2 & H-6). Compound of example 1f was also obtained. Yield, 4.17g (45 %)

Example 3b:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)acetic acid ethyl ester

The title compound was obtained from the compound of example 3a using the procedure described in example 1g. Yield, 1.47g (51%); mp, 186-87°C ($CHCl_3$-PE 60-80°C); MS (ESI^-): 377 (M-1).

Example 3c:

(4-{2-[1-Oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy) - acetic acid ethyl ester

The title compound was obtained from the compound of example 3b using the procedure described in example 1h. The crude product was purified using

flash chromatography (silica gel, 10% CH_3CN+ 0.5 % MeOH in $CHCl_3$). Yield, 81%; mp, 185-186°C; MS (ESI^-): 411 (M-1), analysis: $C_{21}H_{20}N_2O_5S$ requires, C, 61.17; H, 4.85, N, 6.80, S, 7.77; found: C, 61.24; H, 4.68; N, 6.68; S, 8.09%.

Example 3d:

(4-{2-[5-Methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 3c using the procedure described in example 1i. Yield, 85.8%; mp, 180-183°C; MS (ESI+): 449 (M^++Na^+); analysis: $C_{22}H_{24}IN_2O_5S$ requires C, 47.65; H, 4.15, N, 5.05; S, 5.78; found: C, 48.06; H, 4.02; N, 4.73; S, 5.40%.

Example 4:

(4-{2-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)–acetic acid ethyl ester, hemihydrate

Hydroxylamine hydrochloride (0.05g; 0.75 mmol) was added to a solution of the compound of example 3d (0.277g; 0.5 mmol) in ethanol (10 ml), followed by the addition of $NaHCO_3$ (0.063g; 0.75 mmol). The reaction mixture was stirred at room temperature for 1h, concentrated and purified using flash chromatography (silica gel, 3% MeOH in chloroform). Yield, 60%; mp, 175-78°C; MS (ESI): 412 (M^++1); analysis $C_{21}H_{21}N_3O_6$, 0.5 H_2O requires C, 59.96; H, 5.23; N, 10.0; found: C, 60.34, H, 5.16; N, 9.64%.

Example 5:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy) - acetic acid isopropyl ester, hemihydrate

The title compound was obtained from the compound of example 5e using the procedure described in example 1 (propane-2-ol was used instead of methanol). Yield, 46%, mp, 162°C; MS (ESI^+): 410 (M^++1); analysis: $C_{24}H_{27}N_3O_7$, 0.5 H_2O requires C, 60.23; H, 5.90; N, 8.76; found: C, 59.92; H, 5.62; N, 8.61%.

Example 5a:

(4-{2-tert-Butoxycarbonylamino-acetyl}-phenoxy)-acetic acid isopropyl ester

A solution of DCC (2.06g; 10 mmol) in EtOAc (10 ml) was added with stirring, at 0°C to a mixture of the compound of example 1f (2.78g; 9 mmol) and propane-2-ol (2 ml) in EtOAc (20 ml). DMAP (1.1g; 9 mmol) was added after 10 min and stirring continued for 2h at 0°C. The reaction mixture was stored in a freezer overnight. The precipitated DCU was filtered and the filtrate was washed with brine, dried (Na_2SO_4), concentrated and purified using flash chromatography (silica gel, 5% CH_3CN in $CHCl_3$) to obtain the title compound. Yield, 3.0g (94.9%); mp, 62-64°C (EtOAc- PE 60-80°C); analysis: $C_{18}H_{25}NO_6$ requires C, 61.53; H, 7.17; N, 3.99; found: C, 61.94; H, 7.19; N, 3.95%.

Example 5b:

(4-{2-Amino-acetyl}-phenoxy)-acetic acid isopropyl ester, hydrochloride

A mixture of the compound of example 5a (2.5g; 7.12 mmol), formic acid (12 ml) and anisole (0.4 ml) was stirred at room temperature for 4h. Ethereal HCl (1 ml) was added and the reaction mixture was well stirred. It was concentrated, triturated with dry ether, decanted free of ether and thoroughly dried to obtain the title compound. Yield, 1.88g (91.8%); ^1H NMR (D_2O): 1.24 [6H, d, J=7.0, CH ($C\underline{H}_3)_2$], 4.61 (2H, s, $NHC\underline{H}_2$), 4.86 (2H, s, $OC\underline{H}_2CO$), 5.08 (1H, hep, J=7.0, $C\underline{H}Me_2$), 7.05, 7.94 (4H. 2xd, J=8.1, Ar$\underline{H}$).

Example 5c:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid isopropyl ester

The title compound was obtained from the compound of example 5b using the procedure described in example 1g. It was purified using flash chromatography (silica gel, 5% CH_3CN-$CHCl_3$). Yield, 30 %; mp, 147-49°C; analysis: $C_{22}H_{20}N_2O_5$, 0.25 H_2O requires C, 66.51; H, 5.03; N, 7.05; found: C, 66.94; H, 5.14; N, 7.14%.

Example 5d:

(4-{2-[1-Oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)

acetic acid isopropyl ester

The title compound was obtained from the compound of example 5c using the procedure described in example 1h. Yield, 96.77 %; mp, 165°C; MS (ESI^-): 425 (M-1); analysis: $C_{22}H_{22}N_2O_5S$ requires C, 61.96; H, 5.29; N, 6.57; found: C, 62.37; H, 5.39; N, 6.50%.

Example 5e:

(4-{2-[5-Methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid isopropyl ester, hydroiodide

The title compound was obtained from the compound of example 5d using the procedure described in Example 1i. Yield, 79%; mp, 190 (d); MS (ESI^+): 463 (M^++Na).

Example 6:

(4-{2-[5-(Imino-methoxycarbonylamino-methyl)-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-phenoxy)-acetic acid isopropyl ester

Methyl chloroformate (0.023 ml; 0.29 mmol) was added with stirring at 0°C. to a mixture of the compound of example 5 (0.114g; 0.28 mmol), 0.1N aqueous NaOH (2.80 ml; 0.28 mmol) and $NaHCO_3$ (0.024g; 0.28 mmol) in water (3 ml) and dioxan (6 ml). After 1h, the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), concentrated and purified using flash chromatography (silica gel, 3% MeOH-$CHCl_3$). Crystallization was carried out using EtOAc-PE 60-80°C to obtain the title compound. Yield, 0.12g (94.2 %); mp, 183-84°C; MS (ESI^+): 490 (M^++Na^+), 468 (M^++1); analysis: $C_{24}H_{25}N_3O_7$ requires C, 61.66; H, 5.39; N, 8.99; found: C, 61.20; H, 5.23; N, 8.83%.

Example 7:

(4-{2-[5-(Imino-isobutoxycarbonylamino-methyl)-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-phenoxy)-acetic acid isopropyl ester, hemihydrate

The title compound was obtained from the compound of example 5 using the procedure described in example 6 Isobutyl chloroformate was used instead of

methyl chloroformate. Yield, 40%; mp, 155-57°C; MS (ESI^+): 532 (M^++Na^+), 510 (M^++1); analysis: $C_{27}H_{31}N_3O_7$, 0.5 H_2O requires, C, 62.48; H, 6.17; N, 8.11; found, C, 62.62; H, 6.09; N, 7.95%.

Example 8:

(4-{2-[5-(Benzyloxycarbonylamino-imino-methyl)-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-phenoxy)-acetic acid isopropyl ester, hemi hydrate

The title compound was obtained from the compound of example 5 using the procedure described in example 6. Benzyl chloroformate was used instead of methyl chloroformate. Yield, 56%; mp, 156-58°C; MS (ESI^+): 566 (M^++Na^+), 544 (M^++1); analysis: $C_{30}H_{29}N_3O_7$, 0.5 H_2O requires C, 65.22; H, 5.48; N, 7.60; found, C, 65.56; H, 5.42; N, 7.58%.

Example 9:

(4-{2-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy) -acetic acid isopropyl ester, hemihydrate

The title compound was obtained from the compound of example 5e using the procedure described in example 4. Propane-2-ol was used instead of ethanol. Yield, 75.3%; mp, 164-66°C; MS (ESI^+): 448 (M^++Na^+), 426 (M^++1); analysis: $C_{22}H_{25}N_3O_5$, H_2O requires C, 61.50; H, 5.82; N, 9.79; found, C, 61.70; H, 5.39; N, 10.06%.

Example 10:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy) - acetic acid isobutyl ester, hydroiodide

The title compound was obtained from the compound of example 10e using the procedure described in example 1.Isobutanol was used instead of methanol. Yield, 46%; mp, 105°C; MS (CI): 435 (M^++29), 407 (M^++1); analysis: $C_{23}H_{26}N_3O_5I$, requires C, 50.10; H, 4.75; N, 7.62; I, 23.01; found: C, 50.11; H, 5.06; N, 7.28; I, 22.78%.

Example 10a:

(4-{2-[*tert*-Butoxycarbonylamino]-acetyl}-phenoxy)-acetic acid isobutyl ester

The title compound was obtained from the compound of example 1f using the procedure described in example 5a. 2-methyl-1-propanol was used instead of propane-2-ol. Yield, 93.44%; oil; MS (ESI+): 388 (M^++Na), 366 (M^++1), ^{1}H NMR ($CDCl_3$): 0.91 (6H, d, J=7.1, $CH(C\underline{H}_3)_2$], 1.49 [9H, s, $(C\underline{H}_3)_3$], 1.96 (1H, m, $C\underline{H}Me_2$), 4.0 (2H, d, J=7.6, $C\underline{H}_2CHMe_2$), 4.56 (2H, d, J=5.5, $NHC\underline{H}_2$), 4.73 (2H, s, $OC\underline{H}_2CO$), 5.57 (1H, br, N$\underline{H}$), 6.96 (2H, d, J=8.2, H-2 & H-6), 7.96 (2H, d, J=8.2, H-3 & H-5).

Example 10b:

(4-{2-Amino-acetyl}-phenoxy)-acetic acid isobutyl ester, hydrochloride

The title compound was obtained from the compound of example 10a using the procedure described in example 5b. Yield, 89%.

Example 10c:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid isobutyl ester

The title compound was obtained from the compound of example 10b using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 5% CH_3CN-$CHCl_3$). Yield, 25 %; mp, 144-45°C; MS (ESI+): 429 (M^++Na); analysis: $C_{23}H_{22}N_2O_5$, H_2O requires C, 65.02; H, 5.65; N, 6.59; found: C, 65.45; H, 5.32; N, 6.51%.

Example 10d:

(4-{2-[1-Oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy) - acetic acid isobutyl ester

The title compound was obtained from the compound of example 10c using the procedure described in example 1h.The crude product was purified using flash chromatography (silica gel, 1% MeOH in $CHCl_3$). Yield, 95.7%; MS (ESI$^-$): 439 (M-1); analysis: $C_{23}H_{24}N_2O_5S$, requires C, 62.71; H, 5.49; N, 6.36; found: C, 62.90; H, 5.72; N, 6.45%.

Example 10e:

(4-{2-[5-Methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-

acetyl}-phenoxy)-acetic acid isobutyl ester, hydroiodide

The title compound was obtained from the compound of example 10d using the procedure described in example 1i in 73% yield. MS (ESI^+): 478 (M^++Na), 456 (M^++1); ^1H NMR (DMSO-D_6): 0.87 [6H, d, J=7.03, CH ($C\underline{H}_3$)$_2$], 1.96 [1H, m, $CH_2C\underline{H}(CH_3)_2$], 2.85 (3H, s, $SC\underline{H}_3$), 3.94. (2H, d, J=6.4, $C\underline{H}_2CH$ (CH_3)$_2$], 4.64, 4.99, 5.17 (6H, 3xs, 3x$C\underline{H}_2$), 7.14 (2H, d, J=8.3, H-2′ & H-6′), 7.98 (2H, br, H-6, H-7), 8.05 (2H, d, J=8.5, H-3′, H-5′), 8.16 (1H, br, H-4).

Example 11:

(4-{2-[5-(Imino-methoxycarbonylamino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid isobutyl ester

The title compound was obtained from the compound of example 10 using the procedure described in example 6. The crude product was purified using flash chromatography (silica gel with 3% MeOH-$CHCl_3$). Crystallization was carried out using hot EtOAc-PE60-80°C. Yield, 42%; mp, 162-63°C; MS(ESI^+): 504 (M^++Na^+), 482 (M^++1); analysis: $C_{25}H_{27}N_3O_7$ requires C, 62.36; H, 5.65; N, 8.73; found: C, 62.41; H, 5.77; N, 9.08%.

Example 12:

(4-{2-[5-(Imino-isobutoxycarbonylamino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid isobutyl ester, sesquihydrate

The title compound was obtained from the compound of example 10 using the procedure described in example 6 Isobutyl chloroformate was used instead of methyl chloroformate. The crude product was purified using flash chromatography (silica gel, ether/dichloromethane [1:1]) and crystallised using $CHCl_3$-PE60-80°C. Yield, 59%; mp, 140-41°C; MS (ESI^+): 546 (M^-+Na^+), 524 (M^++1); analysis: $C_{28}H_{33}N_3O_7$, requires C, 61.03; H, 6.54; N, 7.63; found, C, 61.16; H, 6.35; N, 7.49%.

Example 13:

(4-{2-[5-(Benzyloxycarbonylamino-imino-methyl)-1-oxo-1,3-dihydro-

isoindol-2-yl]-acetyl}-phenoxy)-acetic acid isobutyl ester

The title compound was obtained from the compound of example 10 using the procedure described in example 6. Benzyl chloroformate was used instead of methyl chloroformate. Yield, 50%; mp, 139-40°C ($CHCl_3$- PE 60-80°C); MS (ESI^+): 580 (M^++Na^+), 558 (M^++1); analysis: $C_{31}H_{31}N_3O_7$, requires C, 66.78; H, 5.60; N, 7.54; found, C, 66.44; H, 5.58; N, 7.22%.

Example 14:

(4-{2-[5-(Imino-methanesulfonylamino-methyl)-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-phenoxy)-acetic acid isobutyl ester

Aqueous 0.1 N NaOH (2.7 ml; 0.27 mmol) was added with stirring over a period of 10 min. to an aqueous solution of the compound of example 10 (0.138g; 0.25 mmol, 4ml) chilled in an ice bath at 0°C. The reaction mixture was extracted with dichloromethane and dried (Na_2SO_4). The dichloromethane layer (10 ml) was decanted, cooled to 0°C, treated with $NaHCO_3$ (0.06g; 0.7 mmol) and subsequently with freshly distilled methanesulfonyl chloride (0.05 ml; 0.64 mmol) under vigorous stirring conditions which was continued for 30 min at 0°C and for 2h at room temperature. The reaction mixture was concentrated and the residue was purified using flash chromatography (silica gel, 2.5% MeOH in chloroform). Crystallisation was carried out using 5% MeOH-$CHCl_3$ and dry ether. Yield, 0.05g (40%); mp, 177-78°C; MS (ESI^+): 524 (M^++Na^+), 502 (M^++1); analysis: $C_{24}H_{27}N_3O_7S$, requires C, 57.47; H, 5.43; N, 8.38, S, 6.39; found, C, 57.88; H, 5.50; N, 8.32; S, 6.78%.

Example 15:

(4-{2-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy) -acetic acid isobutyl ester

The title compound was obtained from the compound of example 10e using the procedure described in example 4. Isobutanol was used instead of EtOH. The crude product was purified using flash chromatography (silica gel, 2.5% MeOH in chloroform). Yield, 74.3%; mp, 153-54°C; MS (ESI^+): 462 (M^++Na^+), 440 (M^++1); analysis: $C_{23}H_{25}N_3O_6$, requires C, 62.86; H, 5.73; N, 9.56;

found, C, 62.58; H, 5.61; N, 9.29%.

Example 16:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid benzyl ester, acetic acid salt, monohydrate

The title compound was obtained from the compound of example 16e using the procedure described in example 1. Isobutanol was used instead of methanol. Yield, 38%; mp, 190°C (d); MS (ESI^+): 480 (M^++Na), 458 (M^++1); analysis: $C_{28}H_{27}N_3O_7$, H_2O requires C, 63.81; H, 5.57; N, 7.97; found: C, 63.59; H, 5.28; N, 7.70%.

Example 16a:

(4-{2-[*tert*-Butoxycarbonylamino]-acetyl}-phenoxy)-acetic acid benzyl ester

A solution of hexamine (7.1g; 50.7 mmol) in chloroform (100 ml) was added to (4-{2-bromo-acetyl}-phenoxy)-acetic acid benzyl ester (18.2g; 50.13 mmol) with stirring at room temperature over a period of 1h. Dry ether (100 ml) was added and the solid hexamine salt obtained was filtered, dried (19g; 37.77 mmol) and hydrolysed with 1.5N HCl (300 ml) for 16h. The mixture was concentrated to a volume of 100 ml, cooled to 0°C and neutralized with $NaHCO_3$. A solution of di-*tert*-butyldicarbonate (12g; 55 mmol) in dioxane (100 ml) was added with stirring and the reaction mixture was allowed to stir, at 0°C for 1h and subsequently at room temperature for 1h. It was concentrated and extracted with EtOAc. The EtOAc layer was washed with brine, dried (Na_2SO_4), concentrated and purified using flash chromatography (silica gel) to obtain the title compound. Yield, 5.4g (27%); MS (CI): 400 (M^++1), 344, 300, 196, 152; ^1H NMR ($CDCl_3$): 1.49 [9H, s, ($C\underline{H}_3)_3$], 4.61 (2H, d, J=5.5. NHC$\underline{H}_2$), 4.76 (2H, s, OC$\underline{H}_2$CO), 5.26 (2H, s, C$\underline{H}_2$Ph) 5.57 (1H, br, N$\underline{H}$), 6.94 , 7.90 (4H, 2xd, J=8.02, Ar$\underline{H}$), 7.32-7.40 (5H, br, $CH_2Ph\underline{H}$).

The acid compound of example1f was obtained in 58% yield.

Example 16b:

(4-{2-Amino-acetyl}-phenoxy)-acetic acid benzyl ester, hydrochloride

The title compound was obtained from the compound of example 16a using the procedure described in example 5b. Yield, 78%; MS (ESI^+): 300 (M^++1); ^1H NMR (DMSO-D_6): 4.51, 5.05, 5.21 (6H, 3xs, 3x$C\underline{H}_2$), 7.12, 7.97 (4H, 2xd, J=8.01, Ar-$\underline{H}$), 7.38 (5H, m, $CH_2Ph\underline{H}$).

Example 16c:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid benzyl ester

The title compound was obtained from the compound of example 16b using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 5% CH_3CN-$CHCl_3$). Yield, 25.4 %; mp, 159-60°C; MS (ESI^+): 463 (M^++Na); analysis: $C_{26}H_{20}N_2O_5$ requires C, 70.90; H, 4.58; N, 6.36; found: C, 70.61; H, 4.49; N, 5.98%.

Example 16d:

(4-{2-[1-Oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy) - acetic acid benzyl ester

The title compound was obtained from the compound of example 16c using the procedure described in example 1h. The crude product was purified using flash chromatography (silica gel, 1% MeOH in $CHCl_3$). Yield, 93%; mp, 137-38°C; MS (ESI^-): 473 (M-1); analysis: $C_{26}H_{22}N_2O_5S$, H_2O requires C, 64.75; H, 4.62; N, 5.62; found: C, 64.52; H, 4.96; N, 5.79%

Example 16e:

(4-{2-[5-Methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid benzyl ester, hydroiodide

The title compound was obtained from the compound of example 16d using the procedure described in example 1i. Yield, 84.2%; ^1H NMR (DMSO-D_6): 2.84 (3H, s, $SC\underline{H}_3$), 4.64, 5.05, 5.17, 5.23 (8H, 4xs, 4x$C\underline{H}_2$), 7.13 (2H, d, J=8.7, H-2′ & H-6′), 7.39 (5H. br, $Ph\underline{H}$), 7.98 (2H, br, H-6, H-7), 8.04 (2H, d, J=8.7, H-3′, H-5′), 8.25 (1H, br, H-4).

Example 17:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-

acetic acid hydrochloride, monohydrate

The compound of example 16 (0.1g) was dissolved in glacial acetic acid (30 ml) at 80°C and the hot solution was hydrogenated using 10% Pd-C (0.01g) for 40 min. The catalyst was filtered off and the filtrate was concentrated to obtain the title compound, which was purified using flash chromatography (RP-18, MeOH-1%AcOH [1:1]). Yield, 0.03g; mp, 302°C; MS: 390 (M^++Na), 368 (M^++1); ^{1}H NMR (TFA): 2.2 (3H, s), 4.77, 4.85, 5.32 (6H, 3xs, 3x$C\underline{H}_2$), 7.05 (2H, d, J=8.02), 8.1 (5H, m).

Alternative method:

The crude compound of example 17 (b) (0.12g) was dissolved in a mixture of formic acid (3 ml) and anisole (0.13 ml). The clear solution was kept at room temperature for 4h. It was stirred with ethereal HCl (0.5 ml) for 2 min., evaporated to dryness and treated with dry ether. The solid obtained was filtered and washed with dry ether. Purification was effected by trituration with MeOH, filtration and drying to obtain the title compound of as a white solid. Yield, 0.04g; mp >250°C(d); MS (ESI$^+$): 368 (M^++1); analysis: $C_{19}H_{18}ClN_3O_5$, H_2O requiresC,56.05;H,4.74;N,9.96;Cl, 8.42; found: C, 54.11; H, 4.66; N, 9.46; Cl, 8.41%.

Example 17a:

(4-{2-[5-(*tert*-Butoxycarbonylamino-imino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

Aqueous 0.1N NaOH (1.2 ml; 1.2 mmol) was added to a solution of the compound of example 3 (0.6g; 1.2 mmol) in dioxane (15 ml) and water (15ml) at 0°C, with stirring, followed by the addition of $NaHCO_3$ (0.11g; 1.2 mmol) and di-*tert*-butyl-dicarbonate (0.35g; 1.44 mmol). The reaction mixture was stirred at 0-10°C for 3h, concentrated, treated with water and extracted with EtOAc. The EtOAc layer was washed with water, dried (Na_2SO_4), concentrated and purified using flash chromatography (silica gel, 20% CH_3CN in chloroform, 2% MeOH in chloroform). Yield, 0.51g (78.3%); ^{1}H NMR (DMSO-D_6): 1.23 (3H, t, J=7.3, $CH_2C\underline{H}_3$), 1.48 [9H, s, $C(C\underline{H}_3)_3$], 4.17 (2H, q, J=7.3, $C\underline{H}_2CH_3$), 4.57, 4.95, 5.14 (6H, 3xs, 3x$C\underline{H}_2$), 7.11 (2H, d, J=8.6, H-2′ & H-6′), 7.81 (1H, d, J=7.3, H-7), 8.05

(3H, m, H-6, H-3′, H-5′), 8.2 (1H, br, H-4), 9.1 (2H, br, 2xNH); MS (ESI^+): 519 (M^++Na), 496 (M^++1).

Example 17b:

(4-{2-[5-(*tert*-Butoxycarbonylamino-imino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid

Aqueous 0.1N NaOH (11.4 ml; 1.14 mmol) was added to a solution of the compound of example 17a (0.375g; 0.756 mmol) in MeOH (10 ml), The reaction mixture was stirred at room temperature for 30 min., acidified with AcOH and concentrated. The crude title compound obtained was filtered, washed with cold water and dried under vacuum. Yield, 140 mg.

Example 18:

(4-{2-[5-(Imino-methoxycarbonylamino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid benzyl ester, hemi hydrate

The title compound was obtained from the compound of example 16 using the procedure described in example 6. The crude product was purified using flash chromatography (silica gel, 3% MeOH-$CHCl_3$). Crystallization was carried out using hot EtOAc-PE 60-80°C. Yield, 40%; mp, 184-86°C; MS (ESI^+): 538 (M^++Na^+), 516 (M^++1); analysis: $C_{28}H_{25}N_3O_7$, 0.5 H_2O requires C, 64.12; H, 4.96; N, 8.02; found: C, 64.36; H, 4.92; N, 8.18%.

Example 19:

(4-{2-[5-(Imino-isobutoxycarbonylamino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid benzyl ester, monohydrate

The title compound was obtained from the compound of example 16 using the procedure described in example 6. Isobutyl chloroformate was used instead of methyl chloroformate.. The crude product was purified using flash chromatography (silica gel, 10% CH_3CN in $CHCl_3$). Crystallization was carried out using $CHCl_3$-PE 60-80°C. Yield, 29%; mp, 162-63°C; MS (ESI^+): 580 (M^++Na^+), 558 (M^++1); analysis: $C_{31}H_{31}N_3O_7$, H_2O requires C, 65.95; H, 5.65; N, 7.42; found, C, 65.94; H, 5.64; N, 7.59%.

Example 20:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-ethoxycarbonyl methoxy-phenoxy)-acetic acid ethyl ester; acetic acid salt, hydrate

The title compound was obtained from the compound of example 20i using the procedure described in example 1. Ethanol was used instead of methanol. mp, 168-69°C; MS (ESI^+): 520 (M^++Na); analysis: $C_{27}H_{31}N_3O_{10}$, H_2O requires C, 56.35; H, 5.74; N, 7.3; found: C, 56.29; H, 5.40; N, 6.97%.

Example 20a:

(2-Ethoxycarbonylmethoxy-phenoxy)-acetic acid ethyl ester

Ethyl 2-bromoacetate (36.5 ml; 165 mmol) was added slowly with stirring at room temperature over a period of 1.5 to a mixture of catechol (16.5g; 150 mmol) and anhydrous K_2CO_3 (55g) in dry DMF (150 ml). The reaction mixture was poured over crushed ice and extracted with EtOAc. The EtOAc layer was washed with water, dried (Na_2SO_4), concentrated and purified using flash chromatography (silica gel, 5% CH_3CN in chloroform) to obtain the title compound. Yield, 38.07g (90%), oil; analysis:. $C_{14}H_{18}O_6$ requires C, 59.57; H, 6.43; found: C, 59.48; H, 6.34 %.

Example 20b:

(4-Acetyl-2-ethoxycarbonylmethoxy-phenoxy)-acetic acid ethyl ester

Perchloric acid (70 % aq.; 1.0 ml) was added slowly to freshly distilled Ac_2O (25 ml) at 0°C. The compound of example 20a (31.8g; 125 mmol) in CH_2Cl_2 (13 ml) was added drop wise at 10-15°C. The reaction mixture was heated on steam bath for 1h, concentrated, poured over crushed ice and $NaHCO_3$ (~ 25g) and extracted with ether. The ether layer was washed with brine, dried (Na_2SO_4), concentrated and purified using flash chromatography (silica gel, 5 % CH_3CN in $CHCl_3$) to obtain the title compound. Yield, 24.6g (61.5 %), semisolid; analysis: $C_{16}H_{20}O_7$: requires C, 59.25; H, 6.22; found: C, 59.57; H, 6.28 %.

Example 20c:

(4-{2-Bromo-acetyl}-2-ethoxycarbonylmethoxy-phenoxy)-acetic acid ethyl ester

Bromine (4.25 ml; 85 mmol) in AcOH: $CHCl_3$ (1:1; 10 ml) was added to a vigorously stirred solution of the compound of example 20b (25.92g; 80 mmol) in AcOH:$CHCl_3$ (1:1; 110 ml) at 55-60°C for 15 min. The mixture was stirred at room temperature for 5 min. and poured over crushed ice and $NaHCO_3$ and extracted with EtOAc. The EtOAc layer was washed with water, dried (Na_2SO_4), concentrated and purified using flash chromatography (silica gel, 3% CH_3CN in chloroform) to obtain the title compound. Yield, 19.34g, (60 %); mp, 84-85°C (EtOAc-PE 60-80°C); analysis: $C_{16}H_{19}O_7Br$: requires C, 47.66; H, 4.75; Br, 19.82; found: C, 48.08; H, 4.82; Br, 19.40 %.

Example 20d:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-2-ethoxycarbonylmethoxy-phenoxy)-acetic acid ethyl ester

Example20e:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-2-carboxymethoxy-phenoxy)-acetic acid

The compound of example 20d (oil) and the compound of example 20e were obtained from the compound of example 20c using the procedure described in example 16a. Yield, (40%); MS (ESI^+): 462 (M^++Na); ^1H NMR ($CDCl_3$): 1.30, (6H, m, 2x$CH_2C\underline{H}_3$), 1.46 [9H, s, $C(C\underline{H}_3)_3$], 4.26 (4H, q, J=7.3, 2x$C\underline{H}_2CH_3$), 4.60 (2H, d, J=5.0, $NHC\underline{H}_2$), 4.77, 4.81 (4H, 2xs, 2x$OC\underline{H}_2$), 5.53 (1H, br, N$\underline{H}$), 6.86 (1H, d, J=8.2, H-6), 7.50 (1H, d, J=1.8, H-3), 7.57 (1H, dd, J=8.2, 1.8, H-5).

The acid compound of example 20e was obtained as a solid. Yield, (50%).

Example 20f:

(4-{2-Amino-acetyl}-2-ethoxycarbonylmethoxy-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 20d using the procedure described in example 5b. Solvent of crystallization: MeOH-ether. Yield, 75%.

Example 20g:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}–2-ethoxy carbonylmethoxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 20e using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 5% CH_3CN-$CHCl_3$). Yield, 22%; mp, 120-21°C; MS (ESI^+): 503 (M^++Na); analysis: $C_{22}H_{20}N_2O_5$, 0.25 H_2O requires C, 66.51; H, 5.03; N, 7.05; found: C, 66.94; H, 5.14; N, 7.14%.

Example 20h:

(2-Ethoxycarbonylmethoxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-iso indol-2-yl]-acetyl}–phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 20g using the procedure described in example 1h. Yield, 75 %; mp, 169-70°C; MS (ESI^+): 537 (M^++Na); analysis: $C_{25}H_{26}N_2O_8S$ requires C, 58.36; H, 5.09; N, 5.44; S, 6.23; found: C, 58.52; H, 5.08; N, 5.11; S, 6.62%.

Example 20i:

(2-Ethoxycarbonylmethoxy-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}–phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 20h using the procedure described in example 1i. Yield, 79%, yellow solid; mp, 168-69°C; MS (ESI^+): 551 (M^++Na); analysis; $C_{26}H_{29}N_2O_8SI$ requires C, 47.56; H, 4.42; N, 4.27; S, 4.88; I, 19.36; found C, 47.72; H, 4.49; N, 4.56; S, 4.69; I, 19.54%.

Example 21:

(2-Ethoxycarbonylmethoxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}–phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 20i using the procedure described in example 4. Yield, 52%; mp, 163-64°C; MS (ESI^-): 536 (M^++1); analysis: $C_{25}H_{27}N_3O_9$, requires C, 58.48; H, 5.30; N, 8.18; found. C, 58.16; H, 5.19; N, 8.08%.

Example 22:

(2-Ethoxycarbonylmethoxy-4-{2-[5-(imino-{3-methyl-butyrylamino}-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}–phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 20 using the procedure described in example 6. Isobutyl chloroformate was used instead of methyl chloroformate. Yield, 24%. mp, 204-05°C; MS (ESI^+): 598 (M^++1); analysis: $C_{30}H_{35}N_3O_{10}$, requires C, 60.29; H, 5.90; N, 7.03; found, C, 60.70; H, 6.28; N, 6.96%.

Example 23:

(2-Ethoxycarbonylmethoxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-1-hydroxyimino-ethyl}–phenoxy)-acetic acid ethyl ester

A mixture of the compound of example 20g (0.14g; 0.3 mmol), hydroxylamine hydrochloride (0.07g; 1.11 mmol) and Na_2CO_3 (0.053g; 0.51 mmol) in ethanol (0.5 ml) and water (1.5 ml) was refluxed in an atmosphere of nitrogen for 1h. The reaction mixture was cooled to room temperature, concentrated and treated with water to obtain the title compound as a white solid which was filtered, washed with cold water and dried. Yield, 0.051g (32.2%); mp, 181-82°C; MS (ESI^+): 551 (M^++Na^+); analysis: $C_{25}H_{28}N_4O_9$, requires C, 56.81; H, 5.34; N, 10.60; found C, 56.33; H, 5.25; N, 10.16 %

Example 24:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}–2-isobutoxy carbonyl methoxy-phenoxy)-acetic acid isobutyl ester, hydroiodide

The title compound was obtained from the compound of example 24e using the procedure described in example 1. Isobutanol was used instead of methanol. Yield, 10%; mp, 95-96°C; MS (ESI^+): 554 (M^++1); analysis: $C_{29}H_{36}IN_3O_8$, requires C, 51.11; H, 5.32; N, 6.17; found: C, 51.42; H, 5.51; N, 6.05%.

Example 24a:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-2-isobutoxycarbonylmethoxy-

phenoxy)-acetic acid isobutyl ester

The title compound (oil) was obtained from the compound of example 20e using the procedure described in example 5a. Isobutanol was used instead of propane-2-ol together with 2.2 equivalents of DCC. Yield, (54%); ^{1}H NMR ($CDCl_3$): 0.91, 0.95 [12H, 2xd, J=8.5, 2xCH($C\underline{H}_3$)$_2$], 1.46 (9H, s, C($C\underline{H}_3$)$_3$], 1.94 (2H, m, 2x$CH_2C\underline{H}M_2$), 3.97 (4H, d, J=6.7, $C\underline{H}_2CHMe_2$), 4.56 (2H, d, J=4.5, NH$C\underline{H}_2$), 4.80, 4.83 (4H, 2xs, 2xO$C\underline{H}_2$), 5.51 (1H, br, N$\underline{H}$), 6.86 (1H, d, J=8.2, H-6), 7.50 (1H, d, J=2.0, H-3), 7.59 (1H, dd, J=8.2, 2.0, H-5).

Example 24b:

(4-{2-Amino-acetyl}-2-isobutoxycarbonylmethoxy-phenoxy)-acetic acid isobutyl ester; hydrochloride

The title compound was obtained from the compound of example 24a using the procedure described in example 5b. Yield, 95%.

Example 24c:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-isobutoxy carbonyl methoxy-phenoxy)-acetic acid isobutyl ester

The title compound was obtained from the compound of example 24b using the procedure described in example 1g.The crude product was purified using flash chromatography (silica gel, 5% CH_3CN-$CHCl_3$). Yield, 21%; mp, 140-41°C; MS (EI): 536 (M^+); analysis: $C_{29}H_{32}N_2O_8$, requires C, 64.91; H, 6.01; N, 5.22; found: C, 65.15; H, 6.06; N, 4.95%.

Example 24d:

(2-Isobutoxycarbonylmethoxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid isobutyl ester

The title compound was obtained from the compound of example 24c using the procedure described in example 1h. Yield, 68 %; mp, 175-76°C; MS (ESI^+): 593 (M^++Na); analysis: $C_{29}H_{34}N_2O_8S$ requires C, 61.04; H, 6.01; N, 4.91; S, 5.62; found: C, 60.84; H, 5.74; N, 4.87; S, 5.40%.

Example 24e:

(2-Isobutoxycarbonylmethoxy-4-{2-[5-methylsulfanylcarbonimidoyl-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid isobutyl ester,

hydroiodide

The title compound was obtained from the compound of example 24d using the procedure described in example 1i. Yield, 87%, yellow solid; MS (ESI^+): 608 (M^++Na).

Example 25:

2-(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-NN-diethyl-acetamide, acetic acid salt

The title compound was obtained from the compound of example 25e using the procedure described in example 1. Yield, 30%; mp, 194-95°C; MS (ESI^+): 423 (M^++1); analysis: $C_{25}H_{30}N_4O_6$ requires: C, 62.23; H, 6.27; N, 11.61; found: C, 62.49; H, 6.18; N, 11.19%.

Example 25a:

(2-{4-Diethylcarbamoylmethoxy-phenyl}-2-oxo-ethyl)-carbamic acid *tert*-butyl ester

Isobutyl chloroformate (0.84 ml; 6.5 mmol) was added to a stirred solution of 4-methyl-morpholine (0.72 ml; 6.5 mmol) and the compound of example 1f (2.0g; 6.5 mmol) in DMF (10 ml) at –25°C, followed by the addition of diethyl amine (0.88 ml; 8.45 mmol). The reaction mixture was stirred for 15 min., poured into a 10% aqueous $NaHCO_3$ solution and extracted with EtOAc. The EtOAc layer was washed with brine, concentrated and crystallized using EtOAc-PE60-80°C to obtain the title compound. Yield, 1.95g (82%); mp, 100-01°C; MS (EI): 364 (M^+), 291, 234 (100%); analysis: $C_{19}H_{28}N_2O_5$ requires C, 62.62; H, 7.74; N, 7.69: found: C, 62.43; H, 7.60; N, 7.25%.

Example 25b:

2-(4-{2-Amino-acetyl}-phenoxy)-N,N diethyl-acetamide, hydrochloride

The title compound was obtained from the compound of example 25a using the procedure described in example 5b. Yield, 95%; mp, 83-84°C; MS (ESI): 265 (M^++1).

Example 25c:

2-(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-N,N-diethylacetamide

The title compound was obtained from the compound of example 25b using the procedure described in example 1g. Yield, 25%; mp, 139-40°C; MS (EI): 405 (M^+); analysis, $C_{23}H_{23}N_3O_4$ requires, C, 68.13; H, 5.72, N, 10.36; found: C, 68.48; H, 5.86; N, 10.34%.

Example 25d:

N, N-Diethyl-2-(4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetamide

The title compound was obtained from the compound of example 25c using the procedure described in example 1h.The crude product was purified using flash chromatography (silica gel, 10% CH_3CN+ 0.5 % MeOH in $CHCl_3$). Yield, 75%, yellow solid; mp, 191-192°C; MS (ESI^+): 462 (M^++Na), analysis: $C_{23}H_{25}N_2O_4S$ requires C, 62.45; H, 5.73, N, 9.56, S, 7.29; found: C, 62.22; H, 5.59; N, 9.31; S, 7.01%.

Example 25e:

2-(2-{4-Diethylcarbamoylmethoxy-phenyl}-2-oxo-ethyl)-1-oxo-2,3-dihydro -1*H*-isoindol-5-carboximidothioic acid methyl ester, hydroiodide

The title compound was obtained from the compound of example 25d using the procedure described in example 1i. Yield, 89%; MS (ESI^+): 452 (M^+-1).

Example 26:

4-(2-{4-[2-(5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl)-acetyl]-phenoxy}-acetoxy)-piperidine-1-carboxylic acid benzyl ester, sesquihydrate

The title compound was obtained from the compound of example 26e using the procedure described in example 1. Propane-2-ol was used instead of methanol. Yield, 28%, white solid; mp, 180-81°C; MS (ESI^+): 585 (M^++1); analysis: $C_{34}H_{36}N_4O_9$ 2.5 H_2O requires: C, 59.21; H, 5.22; N, 8.12; found: C, 58.85; H, 5.23; N, 7.96.

Example 26a:

4-(2-{4-[2-*tert*-Butoxycarbonylamino-acetyl]-phenoxy}-acetoxy)-piperidine-1-carboxylic acid benzyl ester

The compound of example 1f was treated with 4-hydroxy-piperidine-1-carboxylic acid benzyl ester in the presence of DCC as described in the procedure of example 5a to obtain the title compound. The crude material was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 73%; analysis: $C_{28}H_{34}N_2O_8$ requires: C, 63.87; H, 6.51; N, 5.32; found: C, 64.13; H, 6.78; N, 5.02%.

Example 26b:

4-(2-{4-[2-Amino-acetyl]-phenoxy}-acetoxy)-piperidine-1-carboxylic acid benzyl ester, hydrochloride

The title compound was obtained from the compound of example 26a using the procedure described in example 5b. Yield, 80%.

Example 26c:

4-(2-{4-[2-(5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl)-acetyl]-phenoxy}-acetoxy)-piperidine-1-carboxylic acid benzyl ester

The title compound was obtained from the compound of example 26b using the procedure described in example 1g. Yield, 20%; mp, 94-95°C; MS (ESI^-): 566 (M-1); analysis: $C_{32}H_{29}N_3O_7$ requires: C, 67.72; H, 5.15; N, 7.40; found: C, 67.72; H, 5.25; N, 7.06%.

Example 26d:

4-(2-{4-[2-(1-Oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl)-acetyl]-phenoxy}-acetoxy)-piperidine-1-carboxylic acid benzyl ester

The title compound was obtained from the compound of example 26c using the procedure described in example 1h. Yield, 57%; mp, 97-98°C; MS (ESI^+): 624 (M^++Na), 602 (M^++1); analysis: $C_{32}H_{31}N_3O_7S$ requires: C, 63.88; H, 5.19; N, 6.98; S, 5.33; found: C, 63.58; H, 5.14; N, 6.78; S, 5.57%.

Example 26e:

4-(2-{4-[2-(5-Methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl)-acetyl]-phenoxy}-acetoxy)-piperidine-1-carboxylic acid benzyl ester, hydroiodide

The title compound (yellow solid) was obtained from the compound of example 26d using the procedure described in example 1i. Yield, 98%; MS (ESI^+): 638 (M^++Na), 616 (M^++1); ^1H NMR ($CDCl_3$): 1.64, 1.89 (4H, 2xm), 3.14 (3H, s, $SC\underline{H}_3$), 3.33, 3.67 (4H, 2xm), 4.68, 4.73, 5.05 (6H, 3xs, $3xCH_2$), 5.10-5.18 (3H, m, $C\underline{H}_2$ & $COOC\underline{H}$-), 6.99 (2H, d, J=8.6, H-2′ & H-6′), 7.36 (5H, br, $CH_2Ph\underline{H}$), 8.0 (4H, m, H-6, H-7, H-3′ & H-5′), 8.3 (1H, s, H-4).

Example 27:

4-Benzyloxycarbonylamino-2-(4-{2-[5-carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-butyric acid ethyl ester, acetic acid salt

The title compound was obtained from the compound of example 27j using the procedure described in example 1. Ethanol was used instead of methanol. Yield, 38%, white solid; mp, 164-65°C; MS (ESI^+): 573 (M^++1); analysis: $C_{33}H_{36}N_4O_9$ requires C, 62.36; H, 5.70; N, 8.86; found: C, 61.91; H, 5.68; N, 9.20%.

Example 27a:

2-Amino-1-(4-benzyloxy-phenyl)-ethanone, hydrochloride

Hexamine (5.6g; 40 mmol) was added to a solution of 1-(4-benzyloxy-phenyl)-2-bromo-ethanone (12.2g; 40 mmol) in chloroform (80 ml), and stirred for 3h. Dry ether (80 ml) was added and the solid that separated was filtered, washed with ether, dried then suspended in methanol (100 ml) and con. HCl (20 ml) and allowed to stir for16h. The reaction mixture was concentrated, and treated with water (20 ml). The solid obtained was filtered, washed with cold water (2x10 ml) and dried to obtain the title compound. Yield, 10g (89.9%); mp, 228-29°C; MS (EI): 241, 211, 91; analysis: $C_{15}H_{16}ClNO_2$ requires: C, 64.87; H, 5.81; N, 5.04; found: C, 64.86; H, 6.11; N, 5.16%.

Example 27b:

(2-{4-Benzyloxy-phenyl}-2-oxo-ethyl)-carbamic acid *tert*-butyl ester

The compound of example 27a (8.33g; 30 mmol) was dissolved in water (100 ml) and dioxane (100 ml), cooled to 0°C with stirring, and treated with $NaHCO_3$ (5.2g; 65 mmol) and $(Boc)_2O$ (7.2g; 33 mmol). The reaction mixture was

stirred at 0°C for 1h, subsequently at room temperature for 1h and then concentrated. The residue was extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to obtain the title compound which was then crystallized from EtOAc-PE 60-80°C. Yield, 9.5g (92.8%); mp 75-76°C; MS (EI): 341 (M^+), 285, 268, 211, 91; analysis: $C_{20}H_{23}INO_4$ requires: C, 70.36; H, 6.79; N, 4.10; found: C, 70.49; H, 7.22; N, 4.23%.

Example 27c:

(2-{4-Hydroxy-phenyl}-2-oxo-ethyl)-carbamic acid *tert*-butyl ester

The compound of example 27b (6.0g; 17.6 mmol) was dissolved in methanol (60 ml) and hydrogenated using 10% Pd-C (50mg) at 40 psi for 2h. The reaction mixture was filtered, concentrated and purified using flash chromatography (silica gel, 3% CH_3CN in chloroform) to obtain the title compound. Yield, 2.6g (59%); mp, 183-85°C; MS (CI): 252 (M^++1), 196, 178, 152; analysis: $C_{13}H_{17}NO_4$ requires: C, 62.14; H, 6.82; N, 5.57; found: C, 62.23; H, 6.44; N, 5.57%.

Another polar compound was also isolated and characterized as (2-Hydroxy-{2-[4-hydroxy-phenyl]}-ethyl)-carbamic acid *tert*-butyl ester. Yield, 1.5g (25%); mp, 145-46°C; analysis: $C_{13}H_{19}NO_4$ requires: C, 61.64; H, 7.56; N, 5.53; found: C, 62.04; H, 7.91; N, 5.57%.

Example 27d:

4-Benzyloxycarbonylamino-2S-hydroxy buyric acid ethyl ester

Freshly distilled thionyl chloride (5 ml) was added drop wise over a period of 15 min with stirring to a solution of 4-Amino-2S-hydroxy- butyric acid (5g, 42 mmol) in EtOH (100 ml) at 0°C. The reaction mixture was brought to room temperature and stirred overnight (16h). It was concentrated under vacuum to remove all traces of thionyl chloride, treated with water (100 ml), dichloromethane (50 ml) and chilled to 0°C. $NaHCO_3$ (17.5g) was added with stirring, followed by the addition of a solution of 50% benzyl chloroformate in toluene (14.3 ml). The reaction mixture was allowed to stir for 1h at 0°C and subsequently at room temperature for 30 min. The organic layer was separated, washed with brine, dried (Na_2SO_4), concentrated and. purified using flash

chromatography (silica gel, 10% CH_3CN in $CHCl_3$) to obtain the title compound. Yield, 7.7g (65.3%), oil; MS (EI): 281 (M^+), 238, 235, 208, 174; ^1H NMR ($CDCl_3$): 1.29 (3H, t, J=7.5, $CH_2C\underline{H}_3$), 1.86, 2.06 [2H, 2xm, $C\underline{H}_2CH$ (OH)], 3.18 (1H, d, J=6.4 O$\underline{H}$), 3.4 (2H, m, $NHC\underline{H}_2$), 4.22 (2H, q, J=7.7, $C\underline{H}_2CH_3$), 5.12 (2H, s, $C\underline{H}_2Ph$), 5.18 [1H, m, C$\underline{H}$(OH)], 7.3-7.42 (5H, br, Ph$\underline{H}$).

Example 27e:

4-Benzyloxycarbonylamino-2(S)-methanesulfonyloxy-butyric acid ethyl ester

Methanesulfonyl chloride (2.79 ml; 36 mmol) was added drop wise with stirring to a solution of the compound of example 27d (8.4g; 30 mmol) in dichloromethane (90 ml) and pyridine (3.7 ml; 45.98 mmol) at 0°C. The reaction mixture was stirred at 0°C for 2h and subsequently at room temperature overnight (16h). It was processed as is routinely done and was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 6.6g (61.3%); MS (CI): 360 (M^++1); ^1H NMR ($CDCl_3$): 1.30 (3H, t, J=7.3, $CH_2C\underline{H}_3$), 2.28 (2H, 2xm, $NHCH_2C\underline{H}_2$), 3.18 (3H, s, $SO_2C\underline{H}_3$), 3.15, 3.35 (2H, 2xm, $NHC\underline{H}_2$), 4.25 (2H, q, J=7.3, $C\underline{H}_2CH_3$), 5.1 (2H, s, $C\underline{H}_2Ph$), 5.18 [1H, m, C$\underline{H}$(OSO_2Me)], 7.3-7.4 (5H, br, Ph$\underline{H}$).

Example 27f:

4-Benzyloxycarbonylamino-2(S)-(4-{2-*tert*-butoxycarbonylamino-acetyl}-phenoxy)-butyric acid ethyl ester

A mixture of compound of example 27c (4.0g; 16 mmol), compound of example 27e (6.4g; 18 mmol) and K_2CO_3 (4.5g) in DMF (30 ml) was stirred at 65°C for 2.5h. The reaction mixture was brought to room temperature and acidified with 2N HCl (20 ml). It was processed as is routinely done and was purified using flash chromatography (silica gel, 8% CH_3CN in chloroform). Yield, 5.6g (68%), oil; ^1H NMR ($CDCl_3$): 1.23 (3H, t, J=7.6, $CH_2C\underline{H}_3$), 1.5 [9H, s, C($C\underline{H}_3$)$_3$], 2.25 (2H, m, $NHCH_2C\underline{H}_2$), 3.45 (2H, 2xm, $NHC\underline{H}_2CH_2$), 4.22 (2H, q, J=7.6. $C\underline{H}_2CH_3$), 4.58 (2H. d, J=5.5, $NHC\underline{H}_2$), 4.80 (1H, t, J=5.5 N$\underline{H}CH_2CH_2$), 5.1 (2H, s. $C\underline{H}_2Ph$), 5.55 (1H, br, N$\underline{H}CH_2CO$), 6.89 (2H, d, J=8.0, H-3 & H-5), 7.3-7.4 (5H, br, Ph$\underline{H}$). 7.92 (2H, d. J=8.0 H-2 & H-6).

Example 27g:

2-(4-{2-Amino-acetyl}-phenoxy)-4-benzyloxycarbonylamino-butyric acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 27f using the procedure described in example 5b. Yield, 90%; ^{1}H NMR (CD_3OD): 1.28 (3H, t, J=7.3, $CH_2C\underline{H}_3$), 2.22 (2H, m, $NHCH_2C\underline{H}_2$), 3.40 (2H, 2xm, $NHC\underline{H}_2CH_2$), 4.25 (2H, q, J=7.3, $C\underline{H}_2CH_3$), 4.58 (2H, d, J=5.5, $NHC\underline{H}_2$), 5.03 (1H, m, -C<u>H</u>COO), 5.10 (2H, s, $C\underline{H}_2Ph$), 7.08 (2H, d, J=9.0, H-3 & H-5), 7.3-7.8 (5H, br, Ph<u>H</u>) 8.05 (2H, d, J=8.0, H-2 & H-6).

Example 27h:

4-Benzyloxycarbonylamino-2-(4-{2-[5-cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-butyric acid ethyl ester

The title compound was obtained from the compound of example 27g using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 10% CH_3CN in chloroform). Yield, 12%; mp, 152-54°C ($CHCl_3$ -PE 60-80°C); analysis:. $C_{31}H_{29}N_3O_7$ requires C, 67.03; H, 5.22; N, 7.57; found C, 66.83; H, 5.24; N, 7.52%.

Example 27i:

4-Benzyloxycarbonylamino-2-{4-[2-(1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl)-acetyl]-phenoxy}-butyric acid ethyl ester

The title compound was obtained from the compound of example 27h using the procedure described in example 1h. The crude product was purified using flash chromatography (silica gel,10% CH_3CN, 2% MeOH in chloroform). Yield, 93%; mp, 80-81°C : MS (ESI$^-$): 588 (M-1); ^{1}H NMR ($CDCl_3$): 1.25 (3H, t, J=8.8, $CH_2C\underline{H}_3$), 2.24 (2H, m, $NHCH_2C\underline{H}_2$), 3.44 (2H, 2xm, $NHC\underline{H}_2CH_2$), 4.22 (2H, q, J=8.8. $C\underline{H}_2CH_3$), 4.58, 5.02, 5.18 (6H, 3xs. 3x$C\underline{H}_2$), 4.80 (1H, t, $N\underline{H}CH_2$), 5.04 (1H, m, .-C<u>H</u>COO), 6.94 (2H, d, J=8.8, H-2′ & H-6′), 7.35 (5H, br, Ph<u>H</u>), 7.50 (1H, br, $CSN\underline{H}_2$), 7.75-7.78 (3H, m, $CSN\underline{H}_2$, H-6 & H-7), 7.95 (2H, m, H-3′ & H-5′), 8.01 (1H, br, H-4).

Example 27j:

4-Benzyloxycarbonylamino-2-(4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-butyric acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 27i using the procedure described in example 1i. Yield, 95%.

Example 28:

4-Benzyloxycarbonylamino-2-(4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-butyric acid ethyl ester

The title compound was obtained from the compound of example 27j using the procedure described in example 4. Purification was effected using flash chromatography (silica gel, 3% MeOH in chloroform). Yield, 75%; mp, 174-75°C; MS (ESI^-): 611 (M^++Na), 589 (M^++1); analysis: $C_{31}H_{32}N_4O_8$ requires C, 63.26; H, 5.44; N, 9.52; found: C, 62.78; H, 5.28; N, 9.25%.

Example 29:

(4-{2-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenylsulfanyl)-acetic acid methyl ester

The title compound was obtained from the compound of example 29g using the procedure described in example 4. Purification was effected using flash chromatography (silica gel, 3% MeOH in chloroform). Yield, 24% (white solid); mp, 193-94°C; MS (ESI^+): 435 (M^++Na), 414 (M^++1); analysis: $C_{20}H_{19}N_3O_5$ requires C, 58.10; H, 4.63; N, 10.16; S, 7.75; found: C, 58.50; H, 4.67; N, 10.22; S, 7.66%.

Example 29a:

(4-Acetyl-phenylsulfanyl)-acetic acid methyl ester

A mixture of 1-(4-bromo-phenyl)-ethanone (40g, 201 mmol), methyloxycarbonyl methanthiolate copper (I) (40.68g; 241 mmol), quinoline (173 ml) and pyridine (13.6 ml) was heated at 180°C for 2h. The reaction mixture was poured over crushed ice, acidified with conc. HCl and extracted with EtOAc. The EtOAc layer was washed with water, brine, dried (Na_2SO_4), concentrated and purified using flash chromatography (silica gel, 20% EtOAc-PE 60-80°C) to

obtain the title compound. Yield, 20g (44%), oil; MS (EI): 224 (M^+), 209; analysis: $C_{11}H_{12}O_3S$, 0.5 H_2O requires C, 56.65; H, 5.57; found: C, 57.10; H, 5.35%.

Example 29b:

(4-{2-Bromo-acetyl}-phenylsulfanyl)-acetic acid methyl ester

The title compound was obtained from the compound of example 29a using the procedure described in example 20c. Yield, 82%; mp, 113-14°C; MS (EI): (302,304) (M^+), 209; analysis: $C_{11}H_{11}BrO_3S$ requires C, 43.56; H, 3.63; S, 10.56; Br, 26.40; found: C, 43.48; H, 3.67; S, 10.82; Br, 27.82%.

Example 29c:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-phenylsulfanyl)-acetic acid methyl ester:

The title compound was obtained from the compound of example 29b using the procedure described in example 27a-b. Yield, 44%, light yellow gum; MS (ESI^+): 362 (M^++Na), 340 (M^++1); analysis: $C_{16}H_{21}NO_5S$ requires C, 56.62; H, 6.24; N, 4.13; S, 9.45; found: C, 56.40; H, 6.28; N, 4.44; S, 9.88%.

Example 29d:

(4-{2-Amino-acetyl}-phenylsulfanyl)-acetic acid methyl ester, hydrochloride

The title compound was obtained from the compound of example 29c using the procedure described in example 5b. Yield 93%; IR (KBr): 3365, 3000, 1760, 1690, 1600; MS (ESI^+): 240 (M^++1).

Example 29e:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenylsulfanyl)-acetic acid methyl ester

The title compound was obtained from the compound of example 29d using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 3-10% CH_3CN in chloroform). Yield. 17%; mp, 206-07°C; MS (ESI^+): 403 (M^++Na), 381 (M^++1); analysis: $C_{20}H_{15}N_2O_4S$ requires C, 63.15; H, 4.24, N, 7.36; S, 8.43; found: C, 63.07; H, 4.18; N, 7.36; S, 8.84%.

Example 29f:

(4-{2-[1-Oxo-5-thiocarbamoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenylsulfanyl)-acetic acid methyl ester

The title compound was obtained from the compound of example 29e using the procedure described in example 1h. Yield, 70%; mp, 214-15°C; MS (ESI^-): 413 (M-1); analysis: $C_{20}H_{18}N_2O_4S$ requires C, 57.96; H, 4.38, N, 6.76, S, 15.47; found: C, 58.14; H, 4.22; N, 6.67; S, 15.61%.

Example 29g:

(4-{2-[5-Methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenylsulfanyl)-acetic acid methyl ester, hydroiodide

The title compound was obtained from the compound of example 29f using the procedure described in example 1i. Yield, 85%, yellow solid.

Example 30:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-chloro-phenoxy)-acetic acid ethyl ester, acetic acid salt

The title compound was obtained from the compound of example 30h using the procedure described in example 1. Yield, 43%, white solid; mp, 172-73°C; MS (ESI^+): 452 (M^++Na), 430 (M^++1); analysis: $C_{23}H_{24}ClN_3O_7$, $0.5H_2O$; requires C, 55.37; H, 5.01; N, 8.42; Cl, 7.11; found, C, 55.38; H, 4.88; N, 8.18; Cl, 7.46%.

Example 30a:

(2-Chloro-phenoxy)-acetic acid ethyl ester

The title compound was prepared by reacting 2-chloro-phenol, with ethyl 2-bromoacetate and K_2CO_3 in DMF. Yield, 97%, colourless oil; ^1H NMR ($CDCl_3$): 1.29 (3H, t, J=6.3, $CH_2C\underline{H}_3$), 4.29 (2H, q, J=6.3, $C\underline{H}_2CH_3$), 4.72 (2H, s, $OC\underline{H}_2$), 6.76 (1H, d, J=8.2, H-6), 6.95 (1H, m, H-4), 7.20 (1H, m, H-5), 7.40 (1H, dd, J=8.2, H-3).

Example 30b:

(4-Acetyl-2-chloro-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 30a using the procedure described in example 20b. Yield, 10%. Crude product was purified by flash chromatography with 20% EtOAc in PE 60-80°C. mp, 70-71°C; MS (EI): 256 (M^+), 241, 213 155; analysis: $C_{12}H_{13}ClO_4$ requires C, 56.15; H, 5.07;

Cl, 13.82; found, C, 56.24; H, 5.10; Cl, 13.67%.

Example 30c:

(4-{2-Bromo-acetyl}-2-chloro-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 30b using the procedure described in example 20c. Purification was effected using flash chromatography (silica gel, 40% EtOAc in PE60-80°C). Yield, 46%; mp, 128-30°C; MS (EI): (334,336) (M^+), 241; analysis: $C_{12}H_{12}BrClO_4$ requires C, 42.95; H, 3.60; found, C, 42.69; H, 3.45%.

Example 30d:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-2-chloro-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 30c using the procedure described in example 20d. Yield, 20%; mp, 75-76°C; MS (EI): 371 (M^+), 241; analysis: $C_{17}H_{22}ClNO_6$ requires C, 54.91; H, 5.92; N, 3.77; Cl, 9.54; found, C, 55.37; H, 6.00; N, 3.72; Cl, 9.94%.

Example 30e:

(4-{2-Amino-acetyl}-2-chloro-phenoxy)-acetic acid ethyl ester; hydrochloride

The title compound was obtained from the compound of example 30d using the procedure described in example 5b. Yield, 78%; mp, 163-64°C; MS (EI): 271 (M^+), 241; analysis: $C_{12}H_{13}Cl_2NO_4$ requires C, 46.77; H, 4.87; N, 4.55; Cl, 23.03; found, C, 47.12; H, 4.97; N, 4.36; Cl, 22.67%.

Example 30f:

(2-Chloro-4-{2-[5-cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 30e using the procedure described in example 1g. Yield, 11%, white solid; mp. 178-80°C; MS (EI): 412 (M^+), 241; analysis: $C_{21}H_{17}ClN_2O_5$ requires C, 61.10; H, 4.15; N, 6.74; Cl, 8.59; found, C, 60.90; H, 4.23; N, 6.59; Cl, 8.60%.

Example 30g:

(2-Chloro-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-

phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 30F using the procedure described in example 1h. Yield, 86%, yellow solid; mp, 85-87°C; MS (ESI^+): 468 (M^++Na), 446 (M^++1); analysis: $C_{21}H_{19}ClN_2O_5S$ requires C, 56.44; H, 4.29; N, 6.22; Cl, 7.93; S, 7.17; found, C, 56.01; H, 4.30; N, 6.01; Cl, 7.80; S, 7.60%.

Example 30h:

(2-Chloro-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 30g using the procedure described in example 1i. Yield, 91%, yellow solid; mp, 155°C; MS (ESI^+): 468 (M^++Na), 461 (M^++1).

Example 31:

(2-Chloro-4-{2-[5-(imino-isobutoxycarbonylamino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 30 using the procedure described in example 6 Isobutyl chloroformate was used instead of methyl chloroformate. Yield, 42%, white solid; mp, 178-79°C; MS (ESI^+): 552 (M^++Na), 530 (M^++1); analysis: $C_{26}H_{28}ClN_3O_7$ requires C, 58.93; H, 5.19; N, 7.93; Cl, 6.70; found, C, 59.37; H, 5.35; N, 7.98; Cl, 6.39%.

Example 32:

(2-Chloro-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 30h using the procedure described in example 4. Yield, 71%, white solid; mp, 201-02°C; MS (ESI^+): 468 (M^++Na), 446 (M^++1); analysis: $C_{21}H_{20}ClN_3O_5$ requires C, 56.57; H, 4.50; N, 9.43; Cl, 7.96; found, C, 56.53; H, 4.43; N, 9.11; Cl, 8.04%.

Example 33:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-ethyl sulfanyl-phenoxy)-acetic acid ethyl ester, acetic acid salt, monohydrate

The title compound was obtained from the compound of example 33h using the procedure described in example 1. Yield, 24%, white solid; mp, 185-86°C; MS (ESI$^+$): 478 (M^++Na), 456 (M^++1); analysis: $C_{25}H_{29}N_3O_7S$, H_2O requires C, 56.27; H, 5.67; N, 7.88; S, 6.01; found: C, 56.26; H, 5.58; N, 8.20; S, 6.38%.

Example 33a:

1-(3-Ethylsulfanyl-4-hydroxy-phenyl)-ethanone

The title compound was obtained from 1-(3-bromo-4-hydroxy-phenyl)-ethanone using the procedure described in example 29a. 1-Ethanethiolate Cu (I) was used instead of methyloxycarbonylmethanthiolate copper(I). It was purified using flash chromatography (silica gel, 10% EtOAc-PE60-80°C. Yield, 57%, brownish white solid; mp, 88°C; MS (EI): 196 (M^+), 181 (100%); analysis: $C_{10}H_{12}O_2S$ requires C, 61.22; H, 6.12; S, 16.32; found C, 61.54; H, 6.35; S, 16.28%.

Example 33b:

(4-Acetyl-2-ethylsulfanyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 33a using the procedure described in example 20a. The crude product was purified using flash chromatography (silica gel, 10% EtOAc in PE 60-80°C). Yield, 89%, white solid; mp, 64-65°C; MS (ESI): 305 (M^++Na), 283 (M^++1); analysis: $C_{14}H_{18}O_4S$ requires C, 59.57; H, 6.38; S, 11.35; found C, 59.86; H, 6.49; S, 11.47%.

Example 33c:

(4-{2-Bromo-acetyl}-2-ethylsulfanyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 33b using the procedure described in example 20c. Yield, 45%, white solid; mp, 84°C; MS (EI): (360,362) (M^+), 267 (100%); analysis: $C_{14}H_{17}BrO_4S$ requires C, 46.54; H, 4.71; Br, 22.16; S, 8.86; found: C, 46.90; H, 4.84; Br, 21.87; S, 9.31%

Example 33d:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-2-ethylsulfanyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 33c using the procedure described in example 20d. Yield, 29%, white solid; mp, 83°C; MS (EI): 397 (M^+), 267 (100%), 253; analysis: $C_{19}H_{27}NO_6S$ requires C, 57.43; H, 6.80; N, 3.53; S, 8.06; found: C, 57.36; H, 6.80; N, 3.34; S, 8.15%.

Example 33e:

(4-{2-Amino-acetyl}-2-ethylsulfanyl-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 33d using the procedure described in example 5b. Yield, 96%; MS (ESI): 298 (M^++1); ^{1}H NMR (DMSO-D_6): 1.35 (6H, t, J=7.32, 2x$CH_2C\underline{H}_3$), 3.00 (2H, q, J=7.32, $SC\underline{H}_2CH_3$), 4.29 (2H, q, J=7.3, $C\underline{H}_2CH_3$), 4.65 (2H, d, $C\underline{H}_2NH$), 4.80 (2H, s, $OC\underline{H}_2$), 6.75 (1H, d, J=9.14, H-5), 7.30 (3H, br, $N\underline{H}_3$), 7.75 (1H, dd, J=9.14, H-6), 7.90 (1H, br, H-2).

Example 33f:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-ethylsulfanyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 33e using the procedure described in example 1g. Yield, 8%; mp, 157-60°C; MS (ESI^-): 437 (M-1); analysis: $C_{23}H_{22}N_2O_5S$ requires C, 63.01; H, 5.02; N, 6.39; S, 7.31; found: C, 63.26; H, 4.64; N, 6.49; S, 7.64%.

Example 33g:

(2-Ethylsulfanyl-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 33f using the procedure described in example 1h. Yield, 83%; mp, 178-79°C; MS (ESI^+): 495 (M^++Na), 473 (M^++1): analysis: $C_{23}H_{24}N_2O_5S_2$ requires C, 58.46; H, 5.12; N. 5.93; S, 13.57; found: C, 58.40; H, 5.17; N, 5.99; S, 13.62%.

Example 33h:

(2-Ethylsulfanyl-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-

isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 33g using the procedure described in example 1i. Yield, 91%; mp, 182-83°C; MS (ESI^+): 508 (M^++Na), 487 (M^++1);

Example 34:

(2-Ethylsulfanyl-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hemihydrate

The title compound was obtained from the compound of example 33h using the procedure described in example 4. Yield, 85%, white solid; mp, 190-91°C; MS (ESI^+): 494 (M^++Na), 472 (M^++1); analysis: $C_{23}H_{25}N_3O_6S$, $0.5H_2O$, requires C, 57.50; H, 5.42; N, 8.75; S, 6.66; found: C, 57.88; H, 5.32; N, 9.10; S, 6.71%.

Example 35:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-ethane sulfonyl-phenoxy)-acetic acid ethyl ester; acetic acid salt, hydrate

The title compound was obtained from the compound of example 35e using the procedure described in example 1. Yield, 26% (white solid); mp, 174-75°C; MS (ESI^+): 488 (M^++1); analysis: $C_{25}H_{29}N_3O_9S$, H_2O, requires C, 53.10; H, 5.49; N, 7.43; S, 5.75; found: C, 52.40; H, 5.36; N, 7.08; S, 5.68%.

Example 35a:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-2-ethanesulfonyl-phenoxy)-acetic acid ethyl ester

A mixture of compound of example 33d (2.2g; 5.54 mmol) and 3-chloroperbenzoic acid (2.87g; 16.62 mmol) in dichloromethane (10 ml) was stirred at room temperature until all the starting material was consumed. It was processed as is routinely done and was purified using flash chromatography (silica gel, with 5% CH_3CN in chloroform). Yield, 2g (84%), foam; MS (ESI^+): 430 (M^++1); analysis: $C_{19}H_{27}NO_8S$, requires C, 58.14; H, 6.34; N, 3.26; S, 7.46; found: C, 58.51; H, 6.32; N, 3.25; S, 7.40%.

Example 35b:

(4-{2-Amino-acetyl}-2-ethanesulfonyl-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 35a using the procedure described in example 5b Yield, 99%, pale yellow gum; MS (ESI^+): 330 (M^++1); ^1H NMR ($CDCl_3$): 1.30 (6H, t, J=7.32, 2x$CH_2C\underline{H}_3$), 3.50 (2H, q, J=7.32, $SO_2C\underline{H}_2CH_3$), 4.29 (2H, q, J=7.3, $OC\underline{H}_2CH_3$), 4.60 (2H, d, $NHC\underline{H}_2$), 4.90 (2H, s, $OC\underline{H}_2$), 5.50 (1H, br, $N\underline{H}CH_2$), 7.01 (1H, d, J=9.14, H-6), 8.21 (1H, dd, J=9.14, H-5), 8.60 (1H, br, H-3).

Example 35c:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-ethanesulfonyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 35b using the procedure described in example 1g. Yield, 7%; mp, 194-95°C; MS (ESI^-): 469 (M-1); analysis: $C_{23}H_{22}N_2O_7S$ requires C, 58.72; H, 4.68; N, 5.96; S, 6.81; found: C, 58.97; H, 4.64; N, 5.72; S, 6.95%.

Example 35d:

(2-Ethanesulfonyl-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 35c, using the procedure described in example 1h. Yield, 69%, yellow solid; mp, 117-18°C; MS (ESI^+): 527 (M^++Na), 505 (M^++1); analysis: $C_{23}H_{24}N_2O_7S_2$, H_2O requires C, 52.87; H, 4.98; N, 5.36; S, 12.26; found: C, 52.61; H, 4.61; N, 5.35; S, 12.35%.

Example 35e:

(2-Ethanesulfonyl-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 35d using the procedure described in example 1i. Yield, 89%, yellow solid; mp, 198-200°C; MS (ESI^+): 541 (M^++Na), 519 (M^++1).

Example 36:

(2-Ethanesulfonyl-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 35e using the procedure described in example 4. Yield, 70%, white solid; mp, 196-97°C; MS (ESI^+): 526 (M^++Na), 504 (M^++1); analysis: $C_{23}H_{25}N_3O_8S$ requires C, 54.87; H, 4.97; N, 8.35; S, 6.36; found: C, 54.57; H, 4.84; N, 8.05; S, 6.66%.

Example 37:

(2,6-Bis-ethylsulfanyl-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 37h using the procedure described in example 4. Yield, 37%; mp, 183-84°C; MS (ESI^+): 554 (M^++Na), 532 (M^++1); analysis: $C_{25}H_{29}N_3O_6S_2$ requires C, 56.50; H, 5.46; N, 7.90; S, 12.05; found C, 56.90; H, 5.46; N, 8.01; S, 12.30%.

Example 37a:

1-(3,5-Bis-ethylsulfanyl-4-hydroxy-phenyl)-ethanone

Following the procedure for the preparation of example 29a, 1-(3,5-dibromo-4-hydroxy-phenyl)-ethanone was treated with 1-ethanethiolate Cu(I) in place of methyloxycarbonylmethanthiolate copper (I) to obtain 37a. The crude product was purified by flash chromatography with 10% EtOAc in PE 60-80°C. Yield, 16%; mp, 74-75°C; MS (EI): 256 (M^+), 241, 213; analysis: $C_{12}H_{16}O_2S_2$ requires C, 56.25; H, 6.25; S, 25.00; found C, 56.63; H, 6.47; S, 25.39%.

Example 37b:

(4-Acetyl-2,6-bis-ethylsulfanyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 37a using the procedure described in example 20a. It was purified using flash chromatography (silica gel, EtOAc in PE 60-80°C). Yield, 80%, pale yellow liquid; MS (CI): 371 (M^++29), 343 (M^++1), 329; analysis: $C_{16}H_{22}O_4S_2$ requires C, 56.12; H, 6.47; S, 18.72; found C, 56.36; H, 6.42; S, 18.69%.

Example 37c:

(4-{2-Bromo-acetyl}-2,6-bis-ethylsulfanyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 37b using the procedure described in example 20c. The crude product was purified using flash chromatography (silica gel, 10% EtOAc in PE 60-80°C). Yield, 80%, brown gum; MS (EI): (422, 420) (M^+), (319, 317); analysis: $C_{16}H_{21}BrO_4S_2$ requires C, 45.61; H, 5.02; Br, 18.96; S, 15.22; found C, 45.21; H, 4.98; Br, 18.60; S, 15.09%.

Example 37d:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-2,6-bis-ethylsulfanyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 37c using the procedure described in example 27a-b. The crude product was purified using flash chromatography (silica gel, 10% EtOAc in PE 60-80°C). Yield, 48%, pale yellow oil; MS (EI): 457 (M^+), 425, 398; analysis: $C_{21}H_{31}NO_6S_2$ requires C, 55.12; H, 6.83; N, 3.06; S, 14.01; found C, 54.93; H, 6.49; N, 2.98; S, 13.80%.

Example 37e:

(4-{2-Amino-acetyl}-2,6-bis-ethylsulfanyl-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 37d using the procedure described in example 5b. Yield, 72%, yellow semisolid; MS (ESI): 358 (M^++1); analysis: $C_{16}H_{24}ClNO_4S_2$ requires C, 48.78; H, 6.14; N, 3.56; Cl, 9.00; S, 16.28; found C, 48.42; H, 6.05; N, 3.10; Cl, 8.90; S, 15.95%.

Example 37f:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2,6-bis-ethylsulfanyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 37e using the procedure described in example 1g. The crude was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 6%, white solid; MS (ESI): 521 (M^++Na), 499 (M^++1); analysis: $C_{25}H_{26}ClN_2O_5S_2$ requires C, 60.22; H, 5.26; N, 5.62; S, 12.86; found C, 60.68; H, 5.20; N, 5.70; S, 12.90%.

Example 37g:

(2,6-Bis-ethylsulfanyl-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 37f using the procedure described in example 1h. Yield, 51%, yellow solid; mp, 83-84°C; MS (ESI^-): 531 (M-1); analysis: $C_{25}H_{28}N_2O_5S_3$ requires C, 58.37; H, 5.30; N, 5.26; S, 18.06; found C, 58.51; H, 5.40; N, 5.28; S, 18.10%.

Example 37h:

(2,6-Bis-ethylsulfanyl-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester hydroiodide

The title compound was obtained from the compound of example 37g using the procedure described in example 1i. Yield, 98%, yellow solid.

Example 38:

(2-Acetylamino-4-{2-[5-N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 38h using the procedure described in example 1. Yield, 38%; mp, 185-86°C; MS (ESI): 491 (M^++Na), 469 (M^++1); analysis: $C_{23}H_{24}N_4O_7$ requires C, 58.97; H, 5.16; N, 11.96; found: C, 58.85; H, 5.14; N, 11.49%.

Example 38a:

N-(5-Acetyl-2-hydroxy-phenyl)-acetamide

A solution of 1-(4-hydroxy-3-nitro-phenyl)-ethanone (10g) in methanol, DMF (50 ml) and acetic anhydride (10 ml) was hydrogenated using 10% Pd-C (0.45g) for 2h at 30 psi. The catalyst was filtered off. The filtrate was concentrated (5 ml) and treated with EtOAc (100 ml) to obtain the title compound, which was filtered, washed with EtOAc (10 ml) and dried. Yield, 9.1g (85%); mp, >215°C; MS (EI): 193 (M^+), 151, 136, 108.

Example 38b:

(4-Acetyl-2-acetylamino-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 38a using the procedure described in example 20a, which was purified using flash

chromatography (silica gel, 5-10% CH_3CN in chloroform). Yield, 60 %; mp, 113-14°C; MS (ESI): 302 (M^++Na), 280 (M^++1); analysis: $C_{14}H_{17}NO_5$ requires C, 60.21; H, 6.13; N, 5.02; found: C, 60.42; H, 6.24; N, 5.02%.

Example 38c:

(2-Acetylamino-4-{2-bromo-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 38b using the procedure described in example 20c. The crude product was purified using flash chromatography (silica gel, 10% CH_3CN in chloroform). Yield, 64 %; mp, 124-25°C (EtOAc-PE60-80°C); MS (ESI): 380 (M^++Na), 358 (M^++1); analysis: $C_{14}H_{16}BrNO_5$ requires C, 46.95; H, 4.50; N, 3.91; Br, 22.31; found: C, 46.84; H, 4.15; N, 3,54; Br, 22.80%.

Example 38d:

(2-Acetylamino-4-{2-*tert*-butoxycarbonylamino-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 38c using the procedure described in example 20d. The crude product was purified using flash chromatography (silica gel, 3-10% CH_3CN in chloroform). Yield, 35%, oil; ^1H NMR ($CDCl_3$): 1.30 (3H, t, J=7.5, $CH_2C\underline{H}_3$), 1.45 [9H, s, $C(C\underline{H}_3)_3$], 2.27 (3H, s, $NHCOC\underline{H}_3$), 4.30 (2H, q, J=7.5, $C\underline{H}_2CH_3$), 4.63 (2H, d, J=5.4, , $COC\underline{H}_2NH$), 4.74 (2H, s, $OC\underline{H}_2$), 5.5 (1H, br, $N\underline{H}CH_2$), 6.97 (1H, d, J=8.8, H-6), 7.69 (1H, dd, J=8.8, 2.0, H-5), 8.20 (1H, br, J=1.8, H-3), 9.00 (1H, br, $N\underline{H}$).

Example 38e:

(2-Acetylamino-4-{2-amino-acetyl}-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 38d using the procedure described in example 20e. Yield. 90%

Example 38f:

(2-Acetylamino-4-{2-[5-cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 38e using the procedure described in example 1g. The crude product was purified

using flash chromatography (silica gel, 10% CH_3CN in chloroform, 1% MeOH in chloroform). Yield, 16%; mp, 121-22°C.

Example 38g:

(2-Acetylamino-4-{2-[1-oxo-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 38f using the procedure described in example **1h**. The crude product was purified using flash chromatography (silica gel, 10% CH_3CN in chloroform, 1% MeOH in chloroform). Yield, 87%; mp, 110°C.

Example 38h:

(2-Acetylamino-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 38g using the procedure described in example 1i. Yield, 99%.

Example 39:

(2-{Ethoxycarbonylmethyl-methanesulfonyl-amino}-4-{2-[5-(imino-iso butoxycarbonylamino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, mono hydrate

The title compound was obtained from the compound of example 39l using the procedure described in example 6. Isobutyl chloroformate was used instead of methyl chloroformate. Yield, 63%; mp, 80-82°C; MS (ESI): 697 (M^++Na), 675 (M^++1); analysis: $C_{31}H_{38}N_4O_{11}S\ H_2O$ requires, C, 53.75; H, 5.78; N, 8.09; S, 4.62; found C, 53.97; H, 5.57; N, 7.67; S, 4.14%.

Example 39a:

1-(4-Benzyloxy-3-nitro-phenyl)-ethanone

1-(4-hydroxy-3-nitro-phenyl)-ethanone was treated with benzyl bromide in the presence of K_2CO_3 in DMF, and processed as reported in the synthesis of example 20a to obtain the crude product which was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 94%; mp, 132°C; MS (CI): 300 (M^++29), 272 (M^-÷1), 91; analysis: $C_{15}H_{13}NO_4$ requires, C, 66.42; H, 4.83; N, 5.16; found; C, 66.58; H, 4.52; N, 5.30%.

Example 39b:

1-(3-Amino-4-benzyloxy-phenyl)-ethanone

The title compound was obtained from the compound of example 39a using a reported procedure (Boruah. R.N., Ind. J. Chem.,33B, 758, 1994). The crude product was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 76.9%; mp, 124-25°C; MS (EI): 241 (M^+), 150, 91; analysis: $C_{15}H_{15}NO_2$ requires C, 74.67; H, 6.27; N, 5.80; found: C, 74.89; H, 6.45; N, 5.92%.

Example 39c:

N-(5-Acetyl-2-benzyloxy-phenyl)-methanesulfonamide

Methanesulfonyl chloride (6.08 ml; 78.5 mmol) was added drop wise over a period of 30 min. with vigorous stirring to a mixture of compound of example 39b (15.5g; 64.32 mmol) in CH_2Cl_2 (200 ml) and pyridine (13.78 ml; 165.7 mmol) at 0°C,. The reaction mixture was slowly brought to room temperature and stirred overnight (~16h). It was acidified using dil. HCl and extracted with EtOAc. The EtOAc layer was washed with water, brine, dried (Na_2SO_4), concentrated and purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 17.5g (85.3%); mp, 118-19°C; MS (EI): 319 (M^+), 240, 91; analysis: $C_{16}H_{17}NO_4S$ requires C, 60.17; H, 5.36; N, 4.39; S, 10.04; found: C, 60.30; H, 5.40; N, 4.44; S, 10.41%.

Example 39d:

N-(5-Acetyl-2-hydroxy-phenyl)-methanesulfonamide

In an atmosphere of nitrogen 10% Pd-C (1.17g) was added to a mixture of compound of example 39c (11.7g; 36.67 mmol) and ammonium formate (11.56g; 116.23 mmol) in methanol (110 mL) It was refluxed for 3h. The catalyst was filtered and the filtrate concentrated and purified using flash chromatography (silica gel, 10% CH_3CN in chloroform). Yield. 8.3g (84.2%); mp, 202°C: MS (ESI^-): 228 (M-1); analysis: $C_9H_{11}NO_4S$ requires C, 47.15; H, 4.84; N, 6.11; S, 13.98; found: C, 47.39; H, 4.72; N, 6.53; S. 13.53%.

Example 39e:

(4-acetyl-2-{ethoxycarbonylmethyl-methansulfonyl-amino}-phenoxy)-acetic

acid ethyl ester

The title compound was obtained from the compound of example 39d using the procedure described in example 20a. Yield, 56%; MS (ESI): 424 (M^++Na), 402 (M^++1); analysis: $C_{17}H_{23}NO_8S$ requires C, 50.87; H, 5.77; N, 3.49; S, 7.99; found: C, 51.29; H, 6.01; N, 3.08; S, 7.75%.

Example 39f:

(4-{2-Bromoacetyl}-2-{ethoxycarbonylmethyl-methane-sulfonyl-amino}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 39e using the procedure described in example 20c. The crude product was purified using flash chromatography (silica gel, 5-10% CH_3CN in chloroform). Yield, 60%; MS (ESI): 504 (M^++Na), 482 (M^++1); ^1H NMR ($CDCl_3$): 1.32 (6H, m, 2x$CH_2C\underline{H}_3$), 3.16 (3H, s, $SO_2C\underline{H}_3$), 4.18, 4.27 (4H, 2xq, J=6.8, 2x$C\underline{H}_2CH_3$), 4.42, 4.45, 4.84 (6H, 3xs, 3x$C\underline{H}_2$), 6.90 (1H, d, J=8.8, H-3), 8.03 (1H, dd, J=8.5, 1.8, H-4), 8.27 (1H, d, J=1.8, H-6).

Example 39g:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-2-{ethoxycarbonylmethyl-methanesulfonyl-amino}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 39f using the procedure described in example 20d. The crude product was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 28%; mp, 114-15°C; MS (ESI): 538 (M^++Na).

Example 39h:

(4-{2-Amino-acetyl}-2-{ethoxycarbonylmethyl-methanesulfonyl-amino}-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 39g using the procedure described in example 20e. Yield, 90%; mp, 187-90°C; IR (KBr): 2950, 1750, 1600, 1475.

Example 39i:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-ethoxy carbonylmethyl-methanesulfonyl-amino)-phenoxy]-acetic acid ethyl ester

The title compound was obtained from the compound of example 39h

using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 10% CH_3CN in chloroform, 1% MeOH in chloroform). Yield, 20%; mp, 170-71°C; MS (ESI): 580 (M^++Na), 558 (M^++1).

Example 39j:

(2-{Ethoxycarbonylmethyl-methanesulfonyl-amino}-4-{2-[1-oxo-5-thio carbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 39i using the procedure described in example 1h. The crude product was purified using flash chromatography (silica gel, 10% CH_3CN in chloroform, 2% MeOH in chloroform). Yield, 85%; mp, 96°C; MS (ESI): 614 (M^++Na), 592 (M^++1); analysis: $C_{26}H_{29}N_3O_9S_2$ requires, C, 52.78; H, 4.94; N, 7.10; found C, 52.58; H, 4.72; N, 7.49%.

Example 39k:

(2-{Ethoxycarbonylmethyl-methanesulfonyl-amino}-4-{2-[5-methyl sulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 39j using the procedure described in example 1i. Yield, 98%.

Example 39l:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-{ethoxycarbonyl methyl-methanesulfonyl-amino}-phenoxy)-acetic acid ethyl ester, acetic acid salt

The title compound was obtained from the compound of example 39k using the procedure described in example 1. Yield, 25%; ^1H NMR (DMSO-D_6): 1.18, 1.23 (6H, 2xt, J=7.5, $2xCH_2C\underline{H}_3$), 1.78 (3H, s, $C\underline{H}_3COO$), 3.14 (3H, s, $SO_2C\underline{H}_3$), 4.10, 4.20 (4H. 2xq, J=6.8, $2xC\underline{H}_2CH_3$), 4.45, 4.63, 5.11, 5.18 (8H, 4xs, $4xC\underline{H}_2$), 7.28 (1H, d. J=8.9, H-3'), 7.92 (2H, br), 7.92, 8.08, 8.14 (5H, m).

Example 40:

(2-{Ethoxycarbonylmethyl-methanesulfonyl-amino}-4-{2-[5-(N-hydroxy

carbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 39k using the procedure described in example 4. Purification effected using flash chromatography (silica gel, 3% MeOH in chloroform). Yield, 45%; mp, 165-67°C; MS (ESI): 614 (M^++Na), 591 (M^++1); analysis: $C_{26}H_{30}N_4O_{10}S$ requires, C, 52.88; H, 5.12; N, 9.49; S, 5.43; found C, 52.53; H, 5.09; N, 9.06; S, 5.72%.

Example 41:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-phenoxy)-acetic acid ethyl ester, acetic acid salt

The title compound was obtained from the compound of example 41h using the procedure described in example 1. Yield, 40%, white solid; mp, 195-96°C; MS (ESI): 412 (M^++1), analysis: $C_{23}H_{25}N_3O_8$ requires C, 58.60; H, 5.31; N, 8.92; found: C, 58.87; H, 5.36; N, 8.83%.

Example 41a:

(4-acetyl-3-hydroxy-phenoxy)-acetic acid ethyl ester

Example 41b:

(4-acetyl-3-ethoxycarbonylmethoxy-phenoxy)-acetic acid ethyl ester

1-(2,4-dihydroxy-phenyl)-ethanone was treated with 1 equivalent of ethyl 2-bromoacetate and processed as described in the synthesis of example 20a to obtain the desired title compounds. The crude mixture was purified using flash chromatography (silica gel, 3% CH_3CN in chloroform).

41a: Yield, 57%; mp, 76-78°C; MS (EI): 238 (M^+), 223 (100%), 195, 165; analysis: $C_{12}H_{14}O_5$ requires C, 60.50; H, 5.92; found: C, 60.73; H, 5.89%.

41b: Yield 15.4%; mp, 84-84.5°C; MS (EI): 324 (M^+), 309, 253, 223: analysis: $C_{16}H_{20}O_7$ requires C, 59.25; H, 6.22; found: C, 59.49; H, 6.21%.

Example 41c:

(4-{2-Bromo-acetyl}-3-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained by refluxing the compound of example 41a with $CuBr_2$ in EtOAc-$CHCl_3$ (1:1) as reported in the literature (L. C. King et. al. JOC. 1964, 29, 3459).The crude product was purified using flash

chromatography (silica gel, 3% CH_3CN in chloroform) and crystallisation (EtOAc-PE60-80°C). Yield, 54%; mp, 107-08°c; MS (EI): (316, 318) (M^+), 236, 223 (100%); analysis: $C_{12}H_{13}BrO_5$ requires C, 45.45; H, 4.15; found: C, 45.69; H, 4.14%.

Example 41d:

(4-{2-Amino-acetyl}-3-hydroxy-phenoxy)-acetic acid ethyl ester, hydrochloride

Example 41e:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-3-hydroxy-phenoxy)-acetic acid ethyl ester

The compound of example 41c (14.88g) was converted to the hexamine complex (21.5 g), then hydrolyzed with conc. HCl in EtOH using the procedure described in example 1e. The solvent was removed and the residue was stirred with water (50 ml) and filtered. It was washed with cold water (2x5 ml). and dried to give compound of example 41d. Yield, 3.5g (25.8%); mp, 189-92°C (d); analysis: $C_{12}H_{16}ClNO_5$ requires C, 49.75; H, 5.57; N, 4.83; found: C, 49.44; H, 5.93; N, 5.10%.

The filtrate was treated with di-*tert*-butyldicarbonate (13 g) using the procedure described in example 16a. The crude product was purified using flash chromatography (silica gel, 2% CH_3CN in chloroform) to obtain compound of example 41e. Yield, 8.5g (51.7%); mp, 46-48°C; analysis: $C_{17}H_{23}NO_7$ requires C, 57.78; H, 6.56; N, 3.96; found: C, 58.18; H, 6.67; N, 3.86%.

Example 41f:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 41d using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 60%; mp, 193-95°C; MS (EI): 394 (M^+), 223 (100%), 195, 171; analysis: $C_{21}H_{18}N_2O_6$ requires C, 63.96; H, 4.60; N, 7.10; found: C, 63.51; H, 4.57; N, 7.13%.

Example 41g:

(3-Hydroxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl} - phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 41f using the procedure described in example 1h. The crude product was purified using flash chromatography (silica gel, 10% CH_3CN and 2% MeOH in chloroform). Yield, 96%, yellow solid; mp, 227-29°C; MS (ESI): 451 (M^++Na), 429 (M^++1); $C_{21}H_{20}N_2O_6S$ requires C, 58.88; H, 4.67; N, 6.54; S, 7.48; found: C, 59.14; H, 4.68; N, 6.29; S, 7.75%.

Example 41h:

(3-Hydroxy-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 41g using the procedure described in example 1i. Yield, 56%, yellow solid; mp, 167°C (d); MS (ESI): 465 (M^++Na), 443 (M^++1).

Example 42:

(3-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester:

The title compound was obtained from the compound of example 41h using the procedure described in example 4.The crude product was purified using flash chromatography (silica gel, 8% MeOH in chloroform). Yield, 75% (white solid); mp. 197-98°C; MS (ESI^-): 426 (M-1), analysis: $C_{21}H_{21}N_3O_7$ requires C, 59.02; H, 4.92; N, 9.84; found: C, 59.33; H, 4.91; N, 9.44%.

Example 43:

(3-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-phenoxy)-acetic acid benzyl ester

The title compound was obtained from the compound of example 43g using the procedure described in example 4. The crude product was purified using flash chromatography (silica gel, 4% MeOH in chloroform). Yield, 89%, white solid; mp. 183-84°C; MS (ESI^+): 512 (M^++Na), 490 (M^++1); analysis:

$C_{26}H_{23}N_3O_7$ requires C, 63.80; H, 4.74; N, 8.58; found: C, 64.47; H, 4.84; N, 8.63%.

Example 43a:

(4-Acetyl-3-hydroxy-phenoxy)-acetic acid benzyl ester

1-(2,4-Dihydroxy-phenyl)-ethanone was treated with 1 equivalent of benzyl 2-bromoacetate and processed as described in the synthesis of example 20a to obtain the title compound. The crude was purified using flash chromatography (silica gel, 3% CH_3CN in chloroform) and crystallization was effected using ether-PE 60-80°C. Yield, 75%, white solid; mp, 66-67°C; MS (EI): 300 (M^+), 285, 165, 91 (100%); analysis: $C_{17}H_{16}O_5$ requires C, 67.99; H, 5.37; found: C, 67.99; H, 5.53%.

Example 43b:

(4-{2-Bromo-acetyl}-3-hydroxy-phenoxy)-acetic acid benzyl ester

The title compound was obtained from the compound of example 43a using the procedure as described in the synthesis of example 41c The crude product was purified using flash chromatography (silica gel, 1% CH_3CN-chloroform: PE 60-80°C) and crystallized from EtOAc- PE 60-80°C. Yield, 41%; mp, 98-99°C; MS (EI): (380, 378) (M^+), 298, 285; analysis: $C_{17}H_{15}O_5Br$ requires C, 53.85; H, 3.99; Br, 21.07; found: C, 53.70; H, 4:20; Br, 21.46%.

Example 43c:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-3-hydroxy-phenoxy)-acetic acid benzyl ester

The title compound was obtained from the compound of example 43b using the procedure described in example 16a.The crude product was purified using flash chromatography (silica gel, EtOAc PE 60-80°C) and crystallized from EtOAc- PE 60-80°C). Yield, 7%; mp, 97-98°c; MS (CI): 416 (M^++1); analysis: $C_{22}H_{25}NO_7$ requires C, 63.61; H, 6.07; N, 3.37; found: C, 63.48; H, 6.17; N, 3.69%.

Example 43d:

(4-{2-Amino-acetyl}-3-hydroxy-phenoxy)-acetic acid benzyl ester; hydrochloride, sesquihydrate

The title compound was obtained from the compound of example 43c using the procedure described in example 5b. Yield, 91%, white solid; mp, 160-61°c; MS (ESI): 316 (M^++1); analysis: $C_{17}H_{18}ClNO_5$, 1.5 H_2O requires C, 53.86; H, 5.54; N, 3.70; found: C, 54.24; H, 5.82; N, 4.15%.

Example 43e:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-phenoxy)-acetic acid benzyl ester

The title compound was obtained from the compound of example 43d using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel 5% CH_3CN in chloroform). Yield, 24%; mp, 211-13°C; MS (ESI^-): 455 (M-1); analysis: $C_{26}H_{20}N_2O_6$ requires C, 68.42; H, 4.42; N, 6.14; found: C, 68.20; H, 4.09; N, 6.54%.

Example 43f:

(3-Hydroxy-4-{2-[1-oxo-5-thiocarbamoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid benzyl ester

The title compound was obtained from the compound of example 43e using the procedure described in example 1h. The crude product was purified using flash chromatography (silica gel, 10% CH_3CN and 1% MeOH in chloroform). Yield, 83%, yellow solid; mp, 152-53°C; MS (ESI^-): 489 (M-1); analysis: $C_{26}H_{22}N_2O_6S$ requires C, 63.66; H, 4.52; N, 5.71; S, 6.54; found: C, 63.80; H, 4.44; N, 5.64; S, 6.28%.

Example 43g:

(3-Hydroxy-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid benzyl ester, hydroiodide

The title compound was obtained from the compound of example 43f using the procedure described in example 1i. Yield, 94%, yellow solid; ^1H NMR (DMSO-D_6): 2.85 (3H, s, SC<u>H</u>$_3$), 4.65, 5.0, 5.12, 5.22 (8H, 4xs, 4xC<u>H</u>$_2$), 6.55 (1H, br, H-2′), 6.60 (1H, dd, J=8.9, 2.0, H-6′), 7.40 (5H, br, Ph<u>H</u>), 7.72 (1H, d, J=8.9, H-5′), 7.95 (2H, br, H-4 & H-6), 8.10 (1H, d, J=8.7, H-7), 11.60 (1H, s, O<u>H</u>).

Example 44:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-phenoxy)-acetic acid, trifluoroacetate

A mixture of the compound of example 43 (0.08g; 0.163 mmol) and acetic anhydride (0.023 ml; 0.245 mmol) in glacial acetic acid (12 ml) was subjected to hydrogenation over 10% Pd-C (0.02g) at 15 psi for 15 min. Distilled TFA (5 ml) was added to obtain a clear solution. The catalyst was filtered off and the filtrate was evaporated to dryness. The crude product was triturated with acetonitrile and ether twice to afford the title compound as a pure white solid. Yield, 0.045g, (56%); mp, 262°C (d); MS (ESI^+): 384 (M^++1); analysis: $C_{21}H_{18}N_3F_3O_8$, $2H_2O$ requires C, 47.29; H, 4.16; N, 7.88; found: C, 47.57; H, 4.06; N, 7.22%.

Example 45:

(4-{2-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-methoxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 45e using the procedure described in example 4. The crude product was purified using flash chromatography (silica gel, 1-2%MeOH in chloroform). Yield, 25%, white solid; mp, 163-65°C; MS (ESI^+): 464 (M^++Na), 442 (M^++1); analysis: $C_{22}H_{23}N_3O_7$ requires C, 59.86; H, 5.25; N, 9.52; found: C, 59.66; H, 4.92; N, 9.20%.

Example 45a:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-3-methoxy-phenoxy)-acetic acid ethyl ester

To a vigorously stirred solution of the compound of example 41e (4.5g; 12.7 mmol) in dry DMF (20 ml) was added sequentially fused K_2CO_3 (3.5g; 25.5 mmol), methyl iodide (0.96ml; 15.3 mmol) and KF (0.45g). The reaction mixture was stirred for 3h, diluted with water (200 ml) and the oily residue was extracted with chloroform (3x30 ml). The organic layer was washed with brine, dried (Na_2SO_4), concentrated and purified using flash chromatography (silica gel, 3% CH_3CN in chloroform). Yield, 3.25g (69.5%); mp, 75°C; MS (ESI^+): 390 (M^++Na), 368 (M^++1); analysis: $C_{18}H_{25}NO_7$ requires C, 58.85; H, 6.85; N. 3.81; found: C, 58.79; H, 7.26; N, 3.81%.

Example 45b:

(4-{2-Amino-acetyl}-3-methoxy-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 45a using the procedure described in example 5b.

Example 45c:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-methoxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 45b using the procedure described in example 1g.

The crude product was purified using flash chromatography (silica gel, 10% CH_3CN in chloroform). Yield, 28%; mp, 182-83°C; MS (CI): 437 (M^++29), 409 (M^++1); analysis: $C_{22}H_{20}N_2O_6$, 1.5 H_2O requires C, 60.63; H, 5.28; N, 6.43; found: C, 60.97; H, 4.76; N, 6.42%.

Example 45d:

(3-Methoxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy) acetic acid ethyl ester

The title compound was obtained from the compound of example 45c using the procedure described in example 1h.

The crude product was purified using flash chromatography (silica gel, 2% MeOH in chloroform). Yield, 86%; mp, 172°C; MS (ESI$^+$): 465 (M^++Na), 443 (M^++1); analysis: $C_{22}H_{22}N_2O_6S$ requires C, 59.72; H, 5.01; N, 6.33; S, 7.25; found: C, 60.19; H, 5.39; N, 6.21; S, 72%.

Example 45e:

(3-Methoxy-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 45d using the procedure described in example 1i. Yield, 88%, crude product.

Example 46:

(4-{2-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-propoxy-phenoxy)-acetic acid ethyl ester, monohydrate

The title compound was obtained from the compound of example 46e using the procedure described in example 4. The crude product was purified using flash chromatography (silica gel, 1% MeOH in chloroform). Yield, 58%, white solid; mp, 175-77°C; MS (ESI^+): 492 (M^++Na), 470 (M^++1); analysis: $C_{24}H_{27}N_3O_7$, H_2O requires C, 59.13; H, 5.90; N, 8.62; found: C, 59.50; H, 5.48; N, 8.98%.

Example 46a:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-3-propoxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from1-bromopropane and the compound of example 41e using the procedure described in example 45a. The purification was carried out using flash chromatography (silica gel, 3% CH_3CN in chloroform). Yield, 66%, oil; analysis: $C_{20}H_{29}NO_7$ requires C, 60.75; H, 7.39; N, 3.54; found: C, 61.18; H, 7.86; N, 3.81%.

Example 46b:

(4-{2-Amino-acetyl}-3-propoxy-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 46a using the procedure described in example 5b.

Example 46c:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-propoxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 46b using the procedure described in example 1g. Yield, 13%; mp, 132-33°C; MS (ESI^+): 459 (M^++Na), 437 (M^++1).

Example 46d:

(4-{2-[1-Oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-3-propoxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 46c using the procedure described in example 1h. The crude product was purified using flash chromatography (silica gel, 1-2% MeOH in chloroform). Yield, 98%;

mp, 205°C; MS (ESI^-): 469 (M-1).

Example 46e:

(4-{2-[5-Methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-propoxy-phenoxy)-acetic acid ethyl ester; hydroiodide

The title compound was obtained from the compound of example 46d using the procedure described in example 1i. Yield, 98%, crude product.

Example 47:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-ethoxy carbonylmethoxy-phenoxy)-acetic acid ethyl ester, acetic acid salt, monohydrate

The title compound was obtained from the compound of example 47e using the procedure described in example 1. Yield, 13%; mp, 186-88°C; MS (ESI^+): 498 (M^++1); analysis: $C_{29}H_{31}N_3O_{10}$, H_2O requires: C, 57.19; H, 5.82; N, 7.41; found: C, 57.02; H, 5.31; N, 7.55%.

Example 47a:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-3-ethoxycarbonylmethoxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from ethyl 2-bromoacetate and the compound of example 41e using the procedure described in example 45a. Purification was carried out using flash chromatography (silica gel, 2% CH_3CN in chloroform). Yield, 83%, mp, 65-66°C; MS (ESI^+): 462 (M^++Na), 440 (M^++1); analysis: $C_{21}H_{29}NO_7$ requires C, 57.40; H, 6.65; N, 3.19; found: C, 57.82; H, 7.04; N, 3.25%.

Example 47b:

(4-{2-Amino-acetyl}-3-ethoxycarbonylmethoxy-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 47a using the procedure described in example 5b.

Example 47c:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-ethoxy carbonyl

methoxy –phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 47b using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 5-10% CH_3CN in chloroform). Yield, 16%; mp, 135-36°C; MS (ESI^+): 503 (M^++Na), 481 (M^++1); analysis: $C_{25}H_{24}N_2O_8$ requires: C, 62.50; H, 5.03; N, 5.83; found: C, 62.22; H, 4.93; N, 6.33%.

Example 47d:

(3-Ethoxycarbonylmethoxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 47c using the procedure described in example 1h. The crude product was purified using flash chromatography (silica gel, 1-2% MeOH in chloroform. Yield, 70%; MS (ESI^+): 537 (M^++Na), 515 (M^++1).

Example 47e:

(3-Ethoxycarbonylmethoxy-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 47d using the procedure described in example 1i. Yield, 98%, crude product.

Example 48:

(3-Ethoxycarbonylmethoxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 47e using the procedure described in example 4. Yield, 32%; mp, 139-40°C; MS (ESI^+): 536 (M^++Na), 514 (M^++1); analysis: $C_{25}H_{27}N_3O_9$, 0.5 H_2O, requires: C, 57.47; H, 5.17; N, 8.04; found: C, 57.42; H, 5.07; N, 8.21%.

Example 49:

(2-Ethylsulfanyl-3-hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 49g

using the procedure described in example 4. Yield, 42%; mp, 182-83°C; MS (ESI): 510 (M^++Na), 488 (M^++1); analysis: $C_{23}H_{25}N_3O_7S$ requires C, 56.66; H, 5.17; N, 8.62; S, 6.58; found: C, 56.37; H, 5.47; N, 9.01; S, 6.18%.

Example 49a:

1-(3-Ethylsulfanyl-2,4-dihydroxy-phenyl)-ethanone

NBS (53.4g; 0.3 mol) was added over a period of 1h to a solution of 1-(2,4-dihydroxy-phenyl)-ethanone (45.6g; 0.3mol) in acetic acid (300 ml). The reaction mixture was stirred overnight, treated with water (1.5 lit.) and extracted with EtOAc. The EtOAc layer was washed with water, dried (Na_2SO_4), concentrated and purified using flash chromatography (silica gel, 3% CH_3CN in chloroform) to obtain a mixture of bromo compounds viz. 3-bromo, 5-bromo and 3,5-dibromo (53g) and 1-(2,4-dihydroxyphenyl)-1-ethanone (7g).(Purification to separate the bromo compounds resulted in very poor yields).

The mixture was heated with CuSEt, quinoline and pyridine at 160-70°C for 1.5h following a reported procedure (refer R. Adams et. al., JACS, 1951, 81, 4927-31). The crude product was purified using flash chromatography (silica gel, 10% EtOAc in PE60-80°C) to obtain the title compound. Yield, 24%; mp, 42-44°C; MS (EI): 212 (M+), 197, 137, 109; analysis: $C_{10}H_{12}O_3S$ requires C, 56.59; H, 5.70; S, 15.10; found: C, 57.07; H, 6.47; S, 14.83%.

Two other compounds were also isolated:

1-(3,5-Bis-ethylsulfanyl-2,4-dihydroxy-phenyl)-ethanone

Yield, 14%; mp, 55-56°C; MS (EI): 272 (M+), 257, 243, 143; analysis: $C_{17}H_{16}O_3S_2$ requires C, 52.12; H, 5.92; S, 23.54; found: C, 52.48; H, 6.30; S, 23.71%.

1-(5-Ethylsulfanyl-2,4-dihydroxy-phenyl)-ethanone

Yield, 10%; mp, 74-76°C; MS (EI): 212 (M^+), 197, 183, 169, 113; analysis: $C_{10}H_{12}O_3S$ requires C, 56.59; H, 5.70; found: C, 56.72; H, 5.41%.

Example 49b:

(4-Acetyl-2-ethylsulfanyl-3-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 49a using the procedure described in example 20a. It was purified using flash

chromatography (silica gel, 10-20% EtOAc in PE 60-80°C). Yield, 62%; mp, 48-50°C (EtOAc-PE 60-80°C); MS (EI): 298 (M+), 283, 265, 195 (100%); analysis: $C_{14}H_{18}O_5S$ requires C, 56.36; H, 6.08; S, 10.78; found: C, 56.64; H, 6.16; S, 11.38%.

Example 49c:

(4-{2-Bromo-acetyl}-2-ethylsulfanyl-3-hydroxy-phenoxy)-acetic acid ethyl ester

Compound of example 49b was treated with $CuBr_2$ following reported procedure (see example 41c) to obtain the title compound, which was purified using flash chromatography (silica gel, 20% EtOAc in PE 60-80°C, 3% CH_3CN in dichloromethane). Yield, 33%; mp, 121-23°C (EtOAc-PE 60-80°C); MS (EI): (376, 378) (M+), 297, 255, 193 (100%); analysis: $C_{14}H_{17}BrO_5S$ requires C, 44.57; H, 4.54; Br, 21.18; S, 8.50; found: C, 45.22; H, 4.58; Br, 21.29; S, 8.32%.

Example 49d:

(4-{2-Amino-acetyl}-2-ethylsulfanyl-3-hydroxy-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 49c using the procedure described in example 41d. Yield, 51%; mp, 91-92°C; MS (ESI): 336 (M^++Na), 312 (M^++1).

Example 49e:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-ethylsulfanyl-3-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 49d using the procedure described in example 1g. Yield, 26%; mp, 138-40°C; MS (ESI): 477 (M^++Na), 455 (M^++1).

Example 49f:

(2-Ethylsulfanyl-3-hydroxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hemihydrate

The title compound was obtained from the compound of example 49e using the procedure described in example 1h. Yield, 75%; mp, 90°C; MS (ESI): 511 (M^++Na), 489 (M^++1); analysis: $C_{23}H_{24}N_2O_4S_2$, 0.5 H_2O requires C, 55.46; H,

5.02; N, 5.62; found: C, 55.05; H, 4.84; N, 4.94; S, 12.83%.

Example 49g:

(2-Ethylsulfanyl-3-hydroxy-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 49f using the procedure described in example 1i. Yield, 98%.

Example 50:

(2-Ethyl-5-hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 50g using the procedure described in example 4. Yield, 83%; mp, 218-19°C; MS (ESI): 456 (M^++1); analysis: $C_{23}H_{25}N_3O_7$ requires C, 60.65; H, 5.53; N, 9.23; found: C, 60.26; H, 5.51; N, 8.99%.

Example 50a:

(4-Acetyl-2-ethyl-5-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained when 1-(5-Ethyl-2,4-dihydroxy-phenyl)-ethanone was reacted with ethyl 2-bromoacetate, and processed as described in the synthesis of example 20a. Yield, 85.6%; mp, 89-90°C; MS (EI): 266 (M^+), 179.

Example 50b:

(4-{2-Bromo-acetyl}-2-ethyl-5-hydroxy-phenoxy)-acetic acid ethyl ester

The compound of example 50a was treated with $CuBr_2$ following reported procedure (L. C. King et. al., JOC. 1964, 29, 3459-61). Yield, 57.3%; ^{1}H NMR ($CDCl_3$): 1.25 (3H, t, $CH_2C\underline{H}_3$), 1.30 (3H, t. $OCH_2C\underline{H}_3$), 2.65 (2H, q, $C\underline{H}_2CH_3$), 4.25 (2H, q, $OC\underline{H}_2CH_3$), 4.40 (2H, s. $C\underline{H}_2Br$), 4.7 (2H, s, $OC\underline{H}_2$), 6.25 (1H, s, H-6), 7.5 (1H, s, H-3), 12.15 (1H, s, O<u>H</u>).

Example 50c:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-2-ethyl-5-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 50b

using the procedure described in example 27a-b. Yield, 56.3%; ^{1}H NMR ($CDCl_3$): 1.25 (3H, t, $CH_2C\underline{H}_3$), 1.30 (3H, t, $OCH_2C\underline{H}_3$), 1.6, [9H, s, $C(C\underline{H}_3)_3$], 2.65 (2H, q, $C\underline{H}_2CH_3$), 4.25 (2H, q, $OC\underline{H}_2CH_3$), 4.65 (2H, s, $OC\underline{H}_2$), 4.7 (2H, s, $OC\underline{H}_2$), 5.5 (1H, br, N<u>H</u>), 6.25 (1H, s, H-6), 7.45 (1H, s, H-3), 12.0 (1H, s, O<u>H</u>).

Example 50d:

(4-{2-Amino-acetyl}-2-ethyl-5-hydroxy-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 50c using the procedure described in example 5b. Yield 74%.

Example 50e:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-yl]-acetyl}-2-ethyl-5-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 50d using the procedure described in example 1g. Yield, 28%; mp, 209-10°C; MS (EI): 422 (M^+), 251 (100%).

Example 50f:

(2-Ethyl-5-hydroxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 50e using the procedure described in example 1h. The crude product was purified using flash chromatography (silica gel, 1-2% MeOH in chloroform). Yield, 70%; mp, 190-92°C; MS (ESI): 457 (M^++1).

Example 50g:

(2-Ethyl-5-hydroxy-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 50f using the procedure described in example 1i. MS (ESI): 471.5 (M^+) ^{1}H NMR ($CDCl_3$+CD_3OD): 1.20 (3H, t. $CH_2C\underline{H}_3$), 1.25 (3H, t, $OCH_2C\underline{H}_3$), 2.65 (2H, q, $C\underline{H}_2CH_3$), 2.90 (3H, s, $N\underline{H}_2$, O<u>H</u>), 3.0 (3H, s, $SC\underline{H}_3$), 4.25 (2H, q, $OC\underline{H}_2CH_3$), 4.65, 4.70, 5.05 (6H, 3xs, $3xC\underline{H}_2$), 6.25 (1H, s, H-6′), 7.5 (1H, s, H-3′), 7.90 (1H, dd, H-7), 8.05 (1H, d, H-6), 8.15 (1H, s, H-4).

Example 51:

(5-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-2-isopropyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 51g in two steps, using the procedures sequentially, described in example 1i and 4. The crude product was purified using flash chromatography (silica gel, 10-20% CH_3CN in chloroform). Yield, 70%; mp, 207-09°C; MS (ES^+): 492 (M^++Na), 470 (M^++1); analysis: $C_{24}H_{27}N_3O_7$ requires C, 61.40; H, 5.80; N, 8.95; found C, 61.80; H, 5.67; N. 8.93%.

Example 51a:

1-(2,4-Dihydroxy-5-isopropyl-phenyl)-ethanone

Dry HCl was passed through a suspension of 4-isopropyl-1,3-benzenediol (17.01g; 112 mmol), CH_3CN (8.3 ml; 158 mmol) and fused $ZnCl_2$ (14 g) in dry ether (100 ml) for 1h at 0°C. The reaction mixture was then stirred for 1h at room temperature and filtered. The solid obtained was hydrolyzed with boiling water as reported in the literature. The crude product was purified using flash chromatography (silica gel, 3% CH_3CN in chloroform). Yield, 15.2g (69.6%); mp, 142-44°C; MS (CI): 223 (M^++29), 195 (M^++1), 179; analysis: $C_{11}H_{14}O_3$ requires: C, 68.02; H, 7.26; found C, 68.40; H, 7.33%.

Example 51b:

(4-Acetyl-5-hydroxy-2-isopropyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 51a using the procedure described in example 20a. It was purified using flash chromatography (silica gel, chloroform/ PE 60-80°C (1:1) chloroform). Yield, 80%; mp, 70-72°C (EtOAc- PE 60-80°C); MS (EI): 280, 265 (100%), 237, 191; analysis: $C_{15}H_{20}O_5$ requires: C, 64.27; H, 7.19; found C, 64.86; H, 7.47%.

Example 51c:

(4-{2-Bromo-acetyl}-5-hydroxy-2-isopropyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 51b using the procedure described in example 50b. The crude product was purified using flash chromatography (silica gel, 0.5% CH_3CN in chloroform: PE 60-80°C (4:6). Yield, 76%; mp, 94-95°C (EtOAc- PE 60-80°C); 1635; MS (EI): (358,360) (M^+), (343,345), 265 (100%), 237, 191.

Example 51d:
(4-{2-*tert*-Butoxycarbonylamino-acetyl}-5-hydroxy-2-isopropyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 51c using the procedure described in example 27a-b. The crude product was purified using flash chromatography (silica gel, 15% EtOAc in PE 60-80°C). Yield, 47%; mp, 110-11°C (EtOAc- PE 60-80°C); MS (EI): 395 (M^+), 339, 265 (100%); analysis: $C_{20}H_{29}NO_7$ requires C, 60.70; H, 7.39; N, 3.54; found C, 61.11; H, 7.49; N. 2.98%.

Example 51e:
(4-{2-Amino-acetyl}-5-hydroxy-2-isopropyl-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 51d using the procedure described in example 5b. Yield, 88%; MS (EI): 295 (M^+), 265 (100%), 237.

Example 51f:
(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-5-hydroxy-2-iso propyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 51e using the procedure described in example 1g. The crude product was purified by flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 18%; mp, 195-96°C (MeOH-ether); MS (CI): 465 (M^++29), 437 (M^++1), 265, 198, 159; analysis: $C_{24}H_{24}N_2O_6$ requires C, 66.05; H, 5.54; N, 6.42; found C, 66.34; H, 5.83; N. 6.39%.

Example 51g:
(5-Hydroxy-2-isopropyl-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-iso indol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 51f using the procedure described in example 1h. The crude product was purified using flash chromatography (silica gel, 1% MeOH in chloroform). Yield, 76%; mp, 185-86°C (MeOH-ether); MS (ES^-): 469 (M-1); analysis: $C_{24}H_{26}N_2O_6S$ requires C,

61.26; H, 5.57; N, 5.95; S, 6.81; found C, 61.80; H, 5.55; N. 5.72; S, 7.26%.

Example 52:

(2-*tert*-Butyl-5-hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 52g using the procedure described in example 4. Yield, 92%, white solid; mp, 177-78°C; MS (ESI): 506 (M^++Na), 484 (M^++1); analysis: $C_{25}H_{29}N_3O_7$ requires C, 60.91; H, 6.09; N, 8.52; found C, 60.74; H, 6.00; N. 8.45%.

Example 52a:

(4-Acetyl-2-*tert*-butyl)-5-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained when 1-(5-*tert*-Butyl-2,4-dihydroxy-phenyl)-ethanone was treated with ethyl 2-bromoacetate and processed as described in the synthesis of example 20a. Yield, 64%; mp, 110-11°C (EtOAc-PE 60-80°C); MS (CI): 323 (M^++29), 295 (M^++1), 279, 267, 239; analysis: $C_{16}H_{22}O_5$ requires: C, 65.29; H, 7.53; found C, 65.61; H, 7.85%.

Example 52b:

(4-{2-Bromo-acetyl}-2-*tert*-butyl-5-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 52a using the procedure described in example 50b.The crude product was purified using flash chromatography (silica gel, 0.5% CH_3CN in chloroform: PE 60-80°C (4:6)). Yield, 71%; mp, 75-76°C (EtOAc-PE 60-80°C); MS (EI): (372, 374) (M^+), (357, 359), 277; analysis: $C_{16}H_{21}BrO_5$ requires C, 51.49; H, 5.67; Br, 21.41; found C, 51.44; H, 6.19; Br, 21.39%.

Example 52c:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-2-*tert*-butyl-5-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 52b using the procedure described in example 27a-b. The crude product was purified using flash chromatography (silica gel, 15% EtOAc in PE 60-80°C). Yield, 50%, oil; MS (CI): 438 (M^++29), 394, 382, 354 (100%); analysis: $C_{21}H_{31}NO_7$ requires C,

61.60; H, 7.63; N, 3.42; found C, 62.12; H, 7.46; N. 3.24%.

Example 52d:

(4-{2-Amino-acetyl}-2-*tert*-butyl-5-hydroxy-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 52c using the procedure described in example 5b. Yield, 97%; MS (CI): 338 (M^++29), 310 (M^++1), 292, 279; ^{1}H NMR (DMSO-D_6): 1.24 [3H, t, J=7.4, $CH_2C\underline{H}_3$), 1.38 [9H, s, $C(C\underline{H}_3)_3$], 4.22 (2H, q, J=7.4, $C\underline{H}_2CH_3$), 4.37 (2H, d, J=4.5, $NHC\underline{H}_2$), 4.90 (2H, s, $OC\underline{H}_2$), 6.53 (1H, s, H-3), 7.68 (1H, s, H-6), 8.27 (3H, br, $N\underline{H}_3$), 11.41 (1H, s, O$\underline{H}$).

Example 52e:

(2-*tert*-Butyl-4-{2-[5-cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-5-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 52d using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 1-3% CH_3CN in chloroform). Yield, 37%; mp, 192-94°C (EtOAc- PE 60-80°C); MS (EI): 450 (M^+), 279, 251, 193, 171; analysis: $C_{25}H_{26}N_2O_6$ requires C, 66.66; H, 5.82; N, 6.22; found C, 67.12; H, 5.76; N, 6.15%.

Example 52f:

(2-*tert*-Butyl-5-hydroxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 52e using the procedure described in example 1h. The crude product was purified using flash chromatography (silica gel, 10% CH_3CN-1% MeOH in chloroform). Yield, 92%, yellow solid; mp, 203-04°C; MS (ESI): 483 (M^++1), 279, 251, 193, 171; analysis: $C_{25}H_{28}N_2O_6S$ requires C, 61.97; H, 5.82; N, 5.78; S, 6.62: found C, 61.59; H, 5.96; N. 5.76; S, 6.98%.

Example 52g:

(2-*tert*-Butyl-5-hydroxy-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 52f

using the procedure described in example 1i. Yield, 87%, yellow solid; mp, 208-10°C; MS (ESI⁻): 497 (M-1).

Example 53:

(2-Chloro-5-hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hemihydrate

The title compound was obtained from the compound of example 53i using the procedure described in example 4. Yield, 46%; mp, 227-28°C; MS (ESI⁻): 460 (M^+-1); analysis:$C_{21}H_{20}ClN_3O_7$, 0.5 H_2O requires C, 53.52; H, 4.46; N, 8.91; found: C, 53.61; H, 4.42; N, 8.61%.

Example 53a:

1-(5-Chloro-2,4-dihydroxy-phenyl)-ethanone

Example 53b:

1-(3-Chloro-2,4-dihydroxy-phenyl)-ethanone

N-chlorosuccinimide (19.31g; 144.5 mmol) in DMF (20 ml) was added drop wise over a period of 10 min. with stirring to a mixture of 1-(2,4-dihydroxy-phenyl)-ethanone (20g; 131.46 mmol), glacial acetic acid (105 ml) and DMF (26 ml) at 0°C. The reaction mixture was stirred overnight (~16h) at room temperature. It was diluted with water and extracted with EtOAc. The organic layer was washed with water, dried (Na_2SO_4), concentrated and purified using flash chromatography (silica gel, 30% EtOAc in PE 60-80°C). Crystallization using EtOAc- PE 60-80°C gave the pure products.

53a: Yield, 7.7g (31%), white solid; mp, 165-67°C; MS (CI): 187,189 (M^++1).

53b: Yield, 9.4g (38%), white solid; MS (CI): 187,189 (M^++1).

Example 53c:

(4-Acetyl-2-chloro-5-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 53a using the procedure described in example 20a. Yield, 39%, white solid; mp. 140°C; MS (EI): 272 (M^+). 257, 208; analysis: $C_{12}H_{13}ClO_5$ requires C, 52.86; H, 4.81; Cl, 13.00; found: C, 53.33; H, 4.81; Cl, 13.17%.

Example 53d:

(4-{2-Bromo-acetyl}-2-chloro-5-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 53c using the procedure described in example 50b. Yield, 65%, white solid; mp, 112-14°C; MS (EI): (352, 354) (M^+), 257 (100%), 259; analysis: $C_{12}H_{12}BrClO_5$ requires C, 41.00; H, 3.44; halogen, 32.81; found: C, 41.43; H, 3.86; halogen, 33.08%.

Example 53e:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-2-chloro-5-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 53d using the procedure described in example 20d (1.5N ethanolic HCl was used instead of 1.5 N aqueous HCl). Yield, 37%, white solid; mp, 109-10°C; MS (ESI): 410 (M^++Na); analysis: $C_{17}H_{22}ClO_7$ requires C, 52.65; H, 5.72; N, 3.61; Cl, 9.14; found: C, 52.26; H, 5.85; N, 3.93; Cl, 8.89%.

Example 53f:

(4-{2-Amino-acetyl}-2-chloro-5-hydroxy-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 53e using the procedure described in example 5b. Yield, 90%, white solid; mp, 239-41°C (d); MS (ESI): 310 (M^++Na), 288 (M^++1).

Example 53g:

(2-Chloro-4-{2-[5-cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-5-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 53f using the procedure described in example 1g. Yield, 5%, white solid; mp, 214-15°C; MS (CI): 457 (M^++29), 429 (M^++1).

Example 53h:

(2-Chloro-5-hydroxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 53g

using the procedure described in example 1h. Yield, 69%, yellow solid; mp, 227-29°C; MS (ESI): 485 (M^++Na), 463 (M^++1).

Example 53i:

(2-Chloro-5-hydroxy-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 53h using the procedure described in example 1i. Yield, 96%, yellow solid; mp, 173-75°C (d); MS (ESI): 477 (M^++1).

Example 54:

(2-Chloro-3-hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hemihydrate

The title compound was obtained from the compound of example 54g using the procedure described in example 4. Yield, 47%, white solid; mp, 214-15°C; MS (ESI): 484 (M^++Na), 462 (M^++1); analysis: $C_{21}H_{20}ClN_3O_7$, 0.5 H_2O requires C, 53.52; H, 4.46; N, 8.91; found: C, 53.71; H, 4.34; N, 8.74%.

Example 54a:

(4-Acetyl-2-chloro-3-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 53b using the procedure described in example 20a. Yield, 50%, white solid; mp, 110-11°C; MS (CI): 301 (M^++29), 273 (M^++1); analysis: $C_{12}H_{13}ClO_5$ requires C, 52.86; H, 4.81; Cl, 13.00; found: C, 53.42; H, 5.00; Cl, 13.19%.

Example 54b:

(4-{2-Bromo-acetyl}-2-chloro-3-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 54a using the procedure described in example 50b. Yield, 65%, white solid; mp, 137-38°C; MS (EI): (352, 354) (M^+), 259, 257 (100%); analysis: $C_{12}H_{12}BrClO_5$ requires C, 41.00; H, 3.44; halogen, 32.81; found: C, 41.54; H, 3.54; halogen, 33.35%.

Example 54c:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-2-chloro-3-hydroxy-phenoxy)-acetic

acid ethyl ester

The title compound was obtained from the compound of example 54b using the procedure described in example 20d (1.5N ethanolic HCl was used instead of 1.5N aqueous HCl). Yield, 37%, white solid; mp, 109-10°C; MS (CI): 416 (M^++29), 388 (M^++1); analysis: $C_{17}H_{22}ClO_7$ requires C, 52.65; H, 5.72; N, 3.61; Cl, 9.14; found: C, 52.16; H, 5.85; N, 3.93; Cl, 8.89%.

Example 54d:

(4-{2-Amino-acetyl}-2-chloro-3-hydroxy-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 54c using the procedure described in example 5b. Yield, 99%, white solid; mp, 198-200°C; MS (ESI): 288 (M^++1); analysis: $C_{12}H_{14}ClNO_5$ requires C, 43.22; H, 4.80; N, 4.20; Cl, 21.28; found C, 43.04; H, 4.70; N, 4.75; Cl, 21.23%.

Example 54e:

(2-Chloro-4-{2-[5-cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 54d using the procedure described in example 1g. Yield, 4%, white solid; mp, 227-29°C; MS (ESI): 451 (M^++Na), 429 (M^++1); analysis: $C_{21}H_{17}ClN_2O_6$ requires C, 56.38; H, 4.25; N, 6.27; found C, 56.31; H, 4.12; N, 5.87%.

Example 54f:

(2-Chloro-3-hydroxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 54e using the procedure described in example 1h. Yield, 63%, yellow solid; mp, 186-88°C; (ESI): 485 (M^++Na), 463 (M^++1); analysis: $C_{21}H_{19}ClN_2O_6S$ requires C, 54.49; H, 4.14; N, 6.05; found C, 54.09; H, 4.31; N, 5.84%.

Example 54g:

(2-Chloro-3-hydroxy-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 54f

using the procedure described in example 1i. Yield, 86%, yellow solid; mp, 195-97°C; MS (ESI): 477 (M^++1).

Example 55:

(3-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-2-methyl-phenoxy)-acetic acid ethyl ester, hydrate

The title compound was obtained from the compound of example 55f in two steps, using the procedures sequentially, described in examples 1i and 4. Yield, 22%; mp, 226-28°C; MS (ES^+): 464 (M^++Na), 442 (M^++1); analysis: $C_{22}H_{23}N_3O_7$, H_2O requires C, 57.51; H, 5.48; N, 9.15; found C, 57.15; H, 5.11; N. 8.83%.

Example 55a:

1-(2,4-Dihydroxy-3-methyl-phenyl)-ethanone

A mixture of 2-methyl-benzene-1,3-diol, acetic anhydride and $ZnCl_2$ was heated at 150-60°C for 3.5h, and processed as reported in the literature.(Pearson. D. E. et. al., Synthesis, 533, 1972 and the references cited therein). The crude was purified using flash chromatography (silica gel, 0-5% CH_3CN in chloroform) to obtain the title compound. Yield, 73%; mp, 65-66°C (EtOAc- PE 60-80°C); MS (CI): 195 (M^++29), 169 (M^++1); analysis: $C_9H_{10}O_3$ requires C, 65.05; H, 6.07; found C, 65.44; H, 6.62%.

Example 55b:

(4-Acetyl-3-hydroxy-2-methyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 55a using the procedure described in example 20a. The crude was purified using flash chromatography (silica gel, 3% CH_3CN in chloroform). Yield, 87%; mp, 58-60°C (EtOAc-PE 60-80°C); MS (EI): 252 (M^+), 237 (100%), 208, 178, 164; analysis: $C_{13}H_{16}O_5$ requires C, 61.90; H, 6.39; found C, 61.55; H, 6.60%.

Example 55c:

(4-{2-Bromo-acetyl}-3-hydroxy-2-methyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 55b using the procedure described in example 50b. The crude was purified using flash chromatography (silica gel, 1-2% CH_3CN in chloroform). Yield, 61%; mp,

117°C (hot EtOAc-PE 60-80°C); MS (EI): (332, 330) (M^+), 237 (100%), 208.

Example 55d:

(4-{2-Amino-acetyl}-3-hydroxy-2-methyl-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 55c using the procedure described in example 41d. Yield, 86%; mp, 201-03°C; MS (CI): 296 (M^++29), 268 (M^+).

Example 55e:

(4-{2-[5-cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-2-methyl-phenoxy)-acetic acid ethyl ester, hemihydrate

The title compound was obtained from the compound of example 55d using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 21%; mp, 224-25°C (EtOAc- PE60-80°C); MS (EI): 450 (M^+), 279, 251, 193, 171; analysis: $C_{22}H_{20}N_2O_6$, 0.5 H_2O requires C, 63.30; H, 5.07; N, 6.71; found C, 62.99; H, 4.94; N. 6.59%.

Example 55f:

(3-Hydroxy-2-methyl-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 55e using the procedure described in example 1h. The crude product was purified using flash chromatography (silica gel, 25% CH_3CN in chloroform). Yield, 65%; mp, 210-12°C (EtOAc-PE60-80°C); MS (ESI): 465 (M^++Na), 443 (M^++1); analysis: $C_{22}H_{22}N_2O_5S$ requires C, 59.72; H, 5.01; N, 6.33; S, 7.25; found C, 60.05; H, 5.26; N. 6.14; S, 7.57%.

Example 56:

(3-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-2-methyl-phenoxy)-acetic acid benzyl ester, hemihydrate

The title compound was obtained from the compound of example 56f in two steps, using the procedures sequentially, described in examples 1i and 4. Mp, 200°C; MS (ESI): 504 (M^++1); analysis. $C_{27}H_{25}N_3O_7$. 0.5 H_2O requires, C,

63.27; H, 5.11; N, 8.20; found, C, 63.50; H, 4.87; N, 8.16%.

Example 56a:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-3-hydroxy-2-methyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 55d using the procedure described in example 27b. The crude product was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 86%; MS (ESI): 390 (M^++Na), 368 (M^++1).

Example 56b:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-3-hydroxy-2-methyl-phenoxy)-acetic acid

The compound of example 56a was hydrolyzed using 1N methanolic NaOH to obtain the title compound, which was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 82.5%; MS (ESI): 362 (M^++Na), 340 (M^++1).

Example 56c:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-3-hydroxy-2-methyl-phenoxy)-acetic acid benzyl ester

The title compound was obtained from the compound of example 56b using the procedure described in example 5a (benzyl alcohol was used instead of isopropanol). The crude product was purified by flash chromatography (silica gel, 2% CH_3CN in chloroform). Yield, 87.4%; MS (ESI): 475 (M^++Na), 452 (M^++1); analysis. $C_{23}H_{27}NO_7$ requires C, 64.32; H, 6.34; N, 3.26; found, C, 63.67; H, 6.05; N, 3.32%.

Example 56d:

(4-{2-Amino-acetyl}-3-hydroxy-2-methyl-phenoxy)-acetic acid benzyl ester; hydrochloride

The title compound was obtained from the compound of Example 56c using the procedure described in example 5b. Yield, 71%.

Example 56e:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-2-methyl-

phenoxy)-acetic acid benzyl ester

The title compound was obtained from the compound of example 56d using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 38.7%; mp, 212°C; MS (CI): 499 (M^++29), 471 (M^++1), 407, 299, 199, 159, 91 (100%).

Example 56f:

(3-Hydroxy-2-methyl-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid benzyl ester

The title compound was obtained from the compound of example 56e using the procedure described in example 1h. The crude product was purified using flash chromatography (silica gel, 25% CH_3CN in chloroform). Yield, 67.5%, yellow solid; mp, 207°C; analysis $C_{27}H_{24}N_2O_6S$ requires, C, 64.27; H, 4.99; N, 5.55; found, C, 63.28; H, 4.91; N, 5.42%.

Example 57:

(2-Ethyl-3-hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 57g using the procedure described in example 4. Yield, 72%; mp, 196-97°C; analysis: $C_{23}H_{25}N_3O_7$ requires C, 60.65; H, 5.53; N, 9.23; found: C, 60.58; H, 5.75; N, 8.74%.

Example 57a:

(4-Acetyl-2-ethyl-3-hydroxy-phenoxy)-acetic acid ethyl ester

1-(3-Ethyl-2,4-dihydroxy-phenyl)-ethanone was treated with 2-bromo-acetic acid ethyl ester and processed as described in the synthesis of example 20a. Yield, 96.89%; mp, 74-75°C; MS (CI): 267 (M^++1).

Example 57b:

(4-{2-Bromo-acetyl}-2-ethyl-3-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 57a using the procedure described in example 50b. Yield, 47%; ^1H NMR ($CDCl_3$): 1.1 (3H, t, $CH_2C\underline{H}_3$), 1.30 (3H, t. J=7.3, $OCH_2C\underline{H}_3$), 2.75 (2H, q, J=7.3, $CH_2C\underline{H}_3$),

4.25 (2H, q, J=7.3, $OC\underline{H}_2CH_3$), 4.4 (2H, s, $BrC\underline{H}_2$), 4.75 (2H, s, $OC\underline{H}_2CO$), 6.3 (1H, d, J=8.5, H-6), 7.6 (1H, d, J=8.5, H-5), 12.77 (1H, s, 2-O<u>H</u>).

Example 57c:

(4-{2-*tert*-Butoxcarbonylamino-acetyl}-2-ethyl-3-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 57b using the procedure described in example 41e. Yield, 60%; MS (CI): 382 (M+1).

Example 57d:

(4-{2-Amino-acetyl}-2-ethyl-3-hydroxy-phenoxy)-acetic acid ethyl ester; hydrochloride

The title compound was obtained from the compound of example 57c using the procedure described in example 5b. Yield, 65%.

Example 57e:

(4-{2-[5-cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-ethyl-3-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 57d using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 17.4%; mp, 178-79°C; MS (CI): 423 (M^++1).

Example 57f:

(2-Ethyl-3-hydroxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 57e using the procedure described in example 1h. Yield, 86.4%, yellow solid; mp, 156-57°C; MS (ESI^-): 455 (M-1).

Example 57g:

(2-Ethyl-3-hydroxy-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 57f using the procedure described in example 1i. Yield, 98%, yellow solid; mp 74-75°C.

Example 58:

(3-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-2-propyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 58g using the procedure described in example 4. The crude product was purified using flash chromatography (silica gel, 3% MeOH in chloroform). Yield, 70%, white solid; mp, 211-12°C; MS (ESI): 492 (M^++Na), 470 (M^++1); analysis: $C_{24}H_{27}N_3O_7$ requires C, 61.40; H, 5.80; N, 8.95; found C, 61.60; H, 5.84; N, 8.68%.

Example 58a:

(4-Acetyl-3-hydroxy-2-propyl-phenoxy)-acetic acid ethyl ester

1-(2,4-Dihydroxy-3-propyl-phenyl)-ethanone was treated with ethyl 2-bromoacetate and processed as described in the synthesis of example 20a. Yield, 80%, white solid; mp, 61-62°C; MS (EI): 280 (M^+), 265, 251 (100%), 193; analysis: $C_{15}H_{20}O_5$ requires C, 64.27; H, 7.19; found: C, 64.56; H, 7.39%.

Example 58b:

(4-{2-Bromo-acetyl}-3-hydroxy-2-propyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 58a using the procedure described in example 50b. Yield, 50%, white solid; mp, 120-21°C; MS (EI): (358, 360) (M^+), (231, 229), 279, 265 (100%); analysis: $C_{15}H_{19}BrO_5$ requires C, 50.16; H, 5.33; Br, 22.24; found: C, 50.47; H, 5.32; Br, 21.89%.

Example 58c:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-3-hydroxy-2-propyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 58b using the procedure described in example 20b (1.5N ethanolic HCl was used instead of 1.5N aqueous HCl). Yield, 40%, white solid; mp, 80-83°C; MS (CI): 396 (M^++1). 340, 296 (100%); analysis: $C_{20}H_{29}NO_7$ requires C, 60.75; H, 7.39; N, 3.54; found: C, 61.00; H, 7.52; N, 3.52%.

Example 58d:

(4-{2-Amino-acetyl}-3-hydroxy-2-propyl-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 58c using the procedure described in example 5b. Yield, 91%, white solid; mp, 188-190°C; MS (ESI): 288 (M^++1); analysis: $C_{15}H_{22}ClNO_5$ requires C, 54.30; H, 6.68; N, 4.22; Cl, 10.69; found: C, 54.20; H, 6.50; N, 3.98; Cl, 10.50%.

Example 58e:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-2-propyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 58d using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 39%, white solid; mp, 136-37°C; MS (ESI): 437 (M^++1); analysis: $C_{24}H_{24}N_2O_6$ requires C, 66.05; H, 5.54; N, 6.42; found C, 66.05; H, 5.49; N, 6.13%.

Example 58f:

(3-Hydroxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-2-propyl-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 58e using the procedure described in example 1h. Purification was effected using flash chromatography (silica gel, 5% MeOH in chloroform). Yield, 73%, yellow solid; mp, 194-95°C; MS (ESI): 493 (M^++Na), 471 (M^++1); analysis: $C_{24}H_{26}N_2O_6S$ requires C, 61.26; H, 5.57; N, 5.95; S, 6.81; found C, 61.17; H, 5.54; N, 5.75; S, 7.09%.

Example 58g:

(3-Hydroxy-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-2-propyl-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 58f using the procedure described in example 1i. Yield, 98%, yellow solid; MS (ESI): 485 (M^++1); ^1H NMR (DMSO-D_6): 0.90 (3H, t, J=7.6, $CH_2CH_2C\underline{H}_3$), 1.25 (3H, t, J=7.6, $OCH_2C\underline{H}_3$), 1.52 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.65 (2H, t, J=7.6, $C\underline{H}_2CH_2CH_3$),

2.85 (3H, s, SC<u>H</u>$_3$), 4.2 (2H, q, J=7.6, OC<u>H</u>$_2$CH$_3$), 4.65, 5.05, 5.20 (6H, 3xs, 3xC<u>H</u>$_2$), 6.65 (1H, d, J=10.2, H-6'), 7.95 (4H, m), 8.19 (1H, br), 12.2 (1H, s, O<u>H</u>).

Example 59:

(3-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-2-propyl-phenoxy)-acetic acid benzyl ester

The title compound was obtained from the compound of example 59e using the procedure described in example 4. The crude product was purified using flash chromatography (silica gel, 3% MeOH in chloroform). Yield, 80%, white solid; mp, 199-200°C; MS (ESI): 554 (M^++Na), 532 (M^++1); analysis: $C_{29}H_{29}N_3O_7$ requires C, 63.53; H, 5.50; N, 7.91; found C, 65.20; H, 5.48; N, 7.70%.

Example 59a:

(4-{2-*tert*-Butoxycarbonylamino-acetyl}-3-hydroxy-2-propyl-phenoxy)-acetic acid benzyl ester

The compound of example 58c was hydrolyzed using 1N methanolic NaOH. The acid obtained was converted into the title compound as described in the preparation of example 5a. Benzyl alcohol was used instead of isopropanol. Yield, 81%, white solid; mp, 112-13°C; MS (EI): 457 (M^+), 401, 327 (100%), 91; analysis: $C_{25}H_{31}NO_7$ requires C, 65.63; H, 6.83; N, 3.06; found: C, 66.14, H, 6.93; N, 3.07%.

Example 59b:

(4-{2-Amino-acetyl}-3-hydroxy-2-propyl-phenoxy)-acetic acid benzyl ester, hydrochloride

The title compound was obtained from the compound of example 59a using the procedure described in example 5b.

Example 59c:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-2-propyl-phenoxy)-acetic acid benzyl ester

The title compound was obtained from the compound of example 59b using the procedure described in example 1g and was purified using flash

chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 33%, white solid; mp, 198-99°C; MS (ESI): 521 (M^++Na), 499 (M^++1); analysis: $C_{24}H_{26}N_2O_6$ requires C, 69.87; H, 5.26; N, 5.62; found C, 69.97; H, 5.16; N, 5.52%.

Example 59d:

(3-Hydroxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl} -2-propyl-phenoxy)-acetic acid benzyl ester

The title compound was obtained from the compound of example 59c using the procedure described in example 1h. Purification was effected using flash chromatography (silica gel, 10% CH_3CN + 5% MeOH in chloroform). Yield, 91%, yellow solid; mp, 170-71°C; MS (ESI): 555 (M^++Na), 533 (M^++1); analysis: $C_{29}H_{28}N_2O_6S$ requires C, 65.40; H, 5.30; N, 5.26; S, 6.02; found C, 65.76; H, 5.08; N, 5.27; S, 6.39%.

Example 59e:

(3-Hydroxy-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-propyl-phenoxy)-acetic acid benzyl ester, hydroiodide

The title compound was obtained from the compound of example 59d using the procedure described in Example 1i. Yield, 87%, yellow solid; mp, 175-76°C; MS (ESI): 569 (M^++Na), 547 (M^++1); analysis: $C_{30}H_{31}IN_2O_6S$ requires C, 53.42; H, 4.63; N, 4.15; S, 4.75; I. 18.81; found C, 54.08; H, 4.65; N, 4.06; S, 5.07; I, 19.00%.

Example 60:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-2-propyl-phenoxy)-acetic acid, trifluoroacetic acid salt

The compound of example 59 was hydrogenated using 10% Pd-C, as described in example 17. TFA was added to dissolve the precipitated compound. Filtration and concentration afforded the title compound. Yield, 80%, white solid; mp, 222-23°C; MS (ESI): 426 (M^++1); analysis: $C_{24}H_{24}F_3N_3O_8$ requires C, 53.44; H, 4.48; N, 7.79; found C, 52.89; H. 4.70; N, 7.39%.

Example 61:

(4-Hydroxy-3-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 61g using the procedure described in example 4. The crude product was purified by flash chromatography (silica gel, 3% MeOH in chloroform). Yield, 34%, white solid; mp, 158-59°C; MS (ESI): 450 (M^++Na), 428 (M^++1); analysis: $C_{21}H_{21}N_3O_7$ requires C, 59.01; H, 4.95; N, 9.83; found: C, 58.95; H, 5.03; N, 9.58%.

Example 61a:

(3-Acetyl-4-hydroxy-phenoxy)-acetic acid ethyl ester

K_2CO_3 (15.43g; 112 mmol) was added in small portions over 30 min to a solution of 1-(2,5-dihydroxy-phenyl)-ethanone (11.33g; 74.47 mmol) and ethyl 2-bromoacetate (8.29 ml; 75 mmol) in DMF (40 ml). The reaction mixture was stirred at room temperature for 2h, and then processed. The crude product obtained was purified using flash chromatography (silica gel, 2 % CH_3CN in chloroform). Yield, 6.0g (33.8%); mp, 60°C (EtOAc- PE 60-80°C); MS (EI): 238 (M^+), 223, 195, 151 (100%); analysis: $C_{12}H_{14}O_5$ requires C, 60.50; H, 5.92; found: C, 60.57; H, 6.10%.

Example 61b:

(3-{2-Bromo-acetyl}-4-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 61a using the procedure described in example 50b. The crude product was purified using flash chromatography (silica gel, dichloromethane: PE 60-80°C::60:40). Yield, 68%; mp, 120-22°C (EtOAc-PE 60-80°C); MS (EI): 316, 318 (M^+), 236, 223, 195, 163; analysis: $C_{12}H_{13}BrO_5$ requires C, 45.45; H, 4.13; found: C, 45.67; H, 4.16%.

Example 61c:

(3-{2-*tert*-Butoxycarbonylamino-acetyl}-4-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 61b using the procedure described in example 16a (1.5N alcoholic HCl was used

instead of 1.5N aqueous HCl). The crude product was purified by flash chromatography (silica gel, 3% CH_3CN in chloroform). Yield, 52.4%; mp, 91-93°C (EtOAc- PE 60-80°C); MS (ESI^+): 376 (M^++Na), 354 (M^++1); analysis: $C_{17}H_{23}NO_7$ requires C, 57.78; H, 6.56; N, 3.96; found: C, 58.87; H, 6.61; N, 3.66%.

Example 61d:

(3-{2-Amino-acetyl}-4-hydroxy-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 61c using the procedure described in example 5b.

Example 61e:

(3-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-4-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 61d using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 16%; mp, 182°C (EtOAc); MS (ESI^+): 417 (M^++Na), 395 (M^++1); analysis: $C_{21}H_{18}N_2O_6$ requires C, 63.96; H, 4.60; N, 7.10; found: C, 63.83; H, 4.47; N, 7.11%.

Example 61f:

(4-Hydroxy-3-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl} -phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 61e using the procedure described in example 1h. The crude product was purified by flash chromatography with 10% CH_3CN and 1% MeOH in chloroform. Yield, 60%; MS (ESI^+): 451 (M^++Na), 429 (M^++1).

Example 61g:

(4-Hydroxy-3-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 61f using the procedure described in example 1i.

Example 62:

(3-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-5-methoxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 62g using the procedure described in example 4. The crude product was purified using flash chromatography (silica gel, 3% MeOH in chloroform). Yield, 0.061g (73%), white solid; mp, 209-10°C; MS (ESI): 480 (M^++Na), 458 (M^++1), (ESI$^-$): 456 (M-1); analysis: $C_{22}H_{23}N_3O_8$ requires: C, 57.77; H, 5.07; N, 9.19; found: C, 57.36; H, 5.09; N, 9.21%.

Example 62a:

Cyanomethyl-carbamic acid benzyl ester

To a vigorously stirred solution of aminoacetonitrile (20g; 0.216 mole), $NaHCO_3$ (50g; 0.595 mole) in water (450 ml) and dioxane (250 ml), 50% benzyl chloroformate in toluene (67.88 ml; 0.475 mole) was added at 0°C. After stirring at room temperature for 16h, the reaction mixture was extracted with EtOAc. The EtOAc layer was washed with water and dried over anhydrous Na_2SO_4. Solvent was removed and the dark brown oil was purified by flash chromatography over silica gel with 30-50% EtOAc- PE 60-80°C. Yield, 33g (80.3%); mp, 42-43°C; MS (EI): 190 (M^+), 145, 130, 117, 108, 91; analysis: $C_{10}H_{10}N_2O_2$ requires C, 63.15; H, 5.30; N, 14.73; found: C, 62.95; H, 5.05; N, 14.50%.

Example 62b:

(2-{2,4-Dihydroxy-6-methoxy-phenyl}-2-oxo-ethyl)-carbamic acid benzyl ester

Dry HCl gas was passed through a suspension of 5-methoxy-benzene-1,3-diol (11g; 78.49 mmol), 62a (16.42g; 86.36 mmol) and fused $ZnCl_2$ (1.96g) in dry ether (40 ml), for 1h at 0°C. The reaction mixture was kept at 0°C overnight (~16h). The ether was decanted and the yellow residue was hydrolyzed with water as reported in literature (J. S. H. Davies, JCS, 1950, 3206-13). The title compound obtained was purified using flash chromatography (silica gel, 5% CH_3CN-$CHCl_3$.) Yield, 10g (28%); mp, 147-48°C; MS (EI): 331 (M^+), 167 (100%); analysis: $C_{17}H_{17}NO_6$ requires: C, 61.63; H, 5.17; N, 4.23; found: C, 61.20; H, 4.85; N, 4.0%.

Example 62c:

(4-{2-Benzyloxycarbonylamino-acetyl}-3-hydroxy-5-methoxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 62b using the procedure described in example 20a. The crude product was purified using flash chromatography (silica gel, 30% EtOAc-PE 60-80°C). Yield, 6.3g (50%); mp, 113-14°C; MS (EI): 417 (M^+), 253 (100%); analysis: $C_{21}H_{23}NO_8$ requires: C, 61.43; H, 5.55; N, 3.36; found: C, 61.24; H, 4.98; N, 3.63%.

Example 62d:

(4-{2-Amino-acetyl}-3-hydroxy-5-methoxy-phenoxy)-acetic acid ethyl ester, hydrobromide

A mixture of 62c (0.72g, 1.725 mmol), glacial acetic acid (0.353 ml) and 33% HBr in AcOH (1.06 ml) was stirred at room temperature for 30 min. The solvent was removed and the dark brown oil obtained was triturated with dry ether to afford the title compound as a brownish white solid. Yield, 0.6g (95%); mp, 175-76°C; MS (EI): 283 (M^+), 253 (100%); analysis: $C_{13}H_{18}BrNO_8$ requires: C, 42.87; H, 4.98; N, 3.85; Br, 21.94; found:: C, 42.44; H, 5.01; N, 3.68; Br, 22.02%.

Example 62e:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-5-methoxy-phenoxy)-acetic acid ethyl ester, hemihydrate

The title compound was obtained from the compound of example 62d using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 0.156g (6%); mp, 209-10°C.; MS (EI): 424 (M^+), 253 (100%); analysis: $C_{22}H_{20}NO_7.0.5\ H_2O$ requires: C, 60.91; H, 4.85; N, 6.46; found: C, 60.76; H, 4.29; N, 6.37%.

Example 62f:

(3-Hydroxy-5-methoxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, monohydrate

The title compound was obtained from the compound of example 62e using the procedure described in example 1h. The crude product was purified

using flash chromatography (silica gel, 10% CH_3CN, 1% MeOH in chloroform). Yield, 0.143g (91%), yellow solid; mp, 150-52°C; MS (ESI^-): 457 (M-1); analysis: $C_{22}H_{22}N_2O_7$, H_2O requires: C, 55.40; H, 5.04; N, 5.88; S, 6.71; found: C, 55.81; H, 4.93; N, 6.30; S, 7.02%.

Example 62g:

(3-Hydroxy-5-methoxy-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 62f using the procedure described in example 1i. Yield, 0.128g (79%), yellow solid; mp, 152-54°C; MS (ESI^+): 495 (M^++Na), 473 (M^++1); analysis: $C_{23}H_{25}IN_2O_7S$. requires C, 46.01; H, 4.20; N, 4.67; S, 5.34; I, 21.14; found: C, 45.98; H, 4.21; N, 4.86; S, 5.64; I, 21.10%.

Example 63:

(3,5-Dihydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 63h using the procedure described in example 4.The crude product was purified using flash chromatography (silica gel, 3-5% MeOH in $CHCl_3$). Yield, 0.03g (33%), white solid; mp, 229-30°C; MS (ESI^+): 466 (M^++Na), 444 (M^++1), analysis: $C_{21}H_{21}N_3O_8$. requires C, 56.88; H, 4.77; N, 9.48; found: C, 56.50; H, 4.77; N, 8.96%.

Example 63a:

Acetic acid 3-acetoxy-5-benzyloxy-phenyl ester

Water (4.3 ml, 236 mmol) in DMF (20 ml) was added drop wise at room temperature with stirring to a mixture of acetic acid 3,5-diacetoxy-phenyl ester (refer Kawamoto.H. et. al. Synth. Commun. 26, 531, 1996) (35g, 139 mmol), NaH (5.66g, 236 mmol) and benzyl chloride (19.16 ml, 166 mmol) in dry DMF (300 ml). The reaction mixture was stirred overnight (~16h), poured into chilled dil. aqueous HCl and extracted with CH_2Cl_2 to obtain the crude title compound which was purified using flash chromatography (silica ge, 20-50% CH_2Cl_2 in PE 60-

80°C). Yield, 12.5g (30%), white solid; mp: 129-30°C; MS (EI): 300 (M^+), 258, 216, 91 (100%); analysis: $C_{17}H_{16}O_5$ requires: C, 67.99; H, 5.37 found: C, 67.50; H, 5.40%.

Example 63b:

5-Benzyloxy-benzene-1,3-diol

The compound in example 63a was treated with 1N methanolic NaOH for 1h. The reaction mixture was processed and the crude product obtained was purified using flash chromatography (silica gel, 20% EtOAc in PE 60-80°C). Yield, 93%, white solid; mp: 85-86°C; MS (EI): 216 (M^+), 91 (100%); analysis: $C_{13}H_{12}O_3$ requires: C, 72.21; H, 5.59 found: C, 72.51; H, 6.05%.

Example 63c:

(2-{2-Benzyloxy-4,6-dihydroxy-phenyl}-2-oxo-ethyl)-carbamic acid benzyl ester

The title compound was obtained from the compound of example 63b using the procedure described in example 62a-b. The crude product was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 35%, white solid; mp: 129-31°C; MS (ESI^+): 430 (M^++Na), 408 (M^++1), (ESI^-): 406 (M-1); analysis: $C_{23}H_{21}NO_6$ requires: C, 67.81; H, 5.20; N, 3.42; found: C, 67.89; H, 5.10; N, 3.09%.

Example 63d:

(3-Benzyloxy-4-{2-benzyloxycarbonylamino-acetyl}-5-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 63c using the procedure described in example 20a. It was purified using flash chromatography (silica gel, chloroform). Yield, 70%, white solid; mp, 140-41°C; MS (CI): 522. (M^++29), 494 (M^++1); analysis: $C_{27}H_{27}NO_8$ requires: C, 65.71; H, 5.51; N, 2.84; found: C, 66.07; H, 6.03; N, 2.98%.

Example 63e:

(4-{2-Amino-acetyl}-3,5-dihydroxy-phenoxy)-acetic acid ethyl ester, hydrochloride

The compound of example 63d (3.5g; 7.09 mmol) in glacial acetic (150 ml) was hydrogenated using 10% Pd-C (1g) at 15 psi for 30 min. The catalyst was filtered, the filtrate was evaporated to dryness and the crude product obtained

was triturated with ethereal HCl and washed with dry ether to afford the title compound as white solid. Yield, 2g (92%); mp: 225-27°C; MS (ESI$^-$): 268. (M-1); analysis: $C_{12}H_{16}ClNO_6$ requires: C, 47.15; H, 5.28; N, 4.58; Cl, 11.60; found: C, 46.63; H, 5.05; N, 4.29; Cl, 11.50%.

Example 63f:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3,5-dihydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 63e using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 10% CH_3CN, 2% MeOH in $CHCl_3$). Yield, 0.55g (23%), white solid, mp, >260°C; MS (ESI$^+$): 411 (M^++1); analysis: $C_{21}H_{18}N_2O_7$. requires: C, 61.46; H, 4.42; N, 6.83; found: C, 62.24; H, 4.42; N, 6.83%.

Example 63g:

(3,5-Dihydroxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 63f using the procedure described in example 1h. The crude product was purified using flash chromatography (silica gel, 5-10% CH_3CN in $CHCl_3$). Yield, 97%, yellow solid; mp: 260°C (d); MS (ESI$^+$): 467 (M^++Na), 445 (M^++1); analysis: $C_{21}H_{20}N_2O_7S$ requires: C, 56.75; H, 4.54; N, 6.30; S, 7.21; found: C, 57.11; H, 4.72; N, 6.07; S, 7.02%.

Example 63h:

(3,5-Dihydroxy-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 63g using the procedure described in example 1i. Yield, 97%, yellow solid; mp, 95°C.(d); MS (ESI+): 482 (M^++Na), 459 (M^++1).

Example 64:

(2-Ethoxycarbonylmethoxy-3-hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl) -1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-aceic acid ethyl ester

The title compound was obtained from the compound of example 64f in two steps, using the procedures sequentially, described in examples 1i and 4. The crude product was purified using flash chromatography (silica gel, 3% MeOH in chloroform). Yield, 48%, white solid; mp, 153-55°C; MS (ESI): 552 (M^++Na).

Example 64a:

(4-Acetyl-2-ethoxycarbonylmethoxy-3-hydroxy-phenoxy)-acetic acid ethyl ester

1-(2,3,4-Trihydroxy-phenyl)-ethanone was treated with 2-bromo-acetic acid ethyl ester in the presence of K_2CO_3 and processed as described in the synthesis of example 20a. The crude product was purified using flash chromatography (silica gel, 20% EtOAc in PE 60-80°C). Yield, 69.2%, oil; MS (EI): 341 (M^++1), 279, 267, 193, 165; analysis: $C_{16}H_{20}O_8$ requires C, 56.47; H, 5.92; found: C, 56.91; H, 6.32%.

Example 64b:

(4-{2-Bromo-acetyl}-2-ethoxycarbonylmethoxy-3-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 64a using the procedure described in example 50b. The crude product was purified using flash chromatography (silica gel, 20% EtOAc in PE 60-80°C). Yield, 61%; MS (EI): 418, 420 (M^+), 338, 265, 250, 191, and 165.

Example 64c:

[4-(2-*tert*-Butoxycarbonylamino-acetyl)-2-ethoxycarbonylmethoxy-3-hydroxy-phenoxy]-acetic acid ethyl ester

The title compound was obtained from the compound of example 64b using the procedure described in example 20d (1.5N alcoholic HCl was used instead of 1.5N aqueous HCl). The crude product was purified using flash chromatography (silica gel, 20-30% EtOAc in PE 60-80°C). Yield, 58%, oil; MS (ESI^+): 478 (M^++Na), 456 (M^++1); analysis: $C_{21}H_{29}NO_{10}$ requires C, 55.38; H, 6.42; N, 3.06; found: C, 55.78; H, 6.85; N, 3.43%.

Example 64d:

[4-(2-Amino-acetyl)-2-ethoxycarbonylmethoxy-3-hydroxy-phenoxy]-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 64c using the procedure described in example 5b.

Example 64e:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-ethyoxy carbonylmethoxy-3-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 64d using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 5%CH_3CN in chloroform). Yield, 14%; mp, 136-38°C (EtOAc); MS (ESI^-): 495 (M-1).

Example 64f:

(2-Ethoxycarbonylmethoxy-3-hydroxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 64e using the procedure described in example 1h. The crude product was purified using flash chromatography (silica gel, 10% CH_3CN, 1% MeOH in chloroform). Yield 72%; mp, 76°C; MS (ESI^+): 553 (M^++Na); analysis: $C_{25}H_{26}N_2O_9S$ requires C, 56.60; H, 4.94; N, 5.28; found: C, 57.02; H, 4.62; N, 5.03 %.

Example 65:

(2-Ethoxycarbonylmethoxy-5-hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, sesquihydrate

The title compound was obtained from the compound of example 65i in two steps, using the procedures sequentially, described in examples 1i and 4. It was purified using flash chromatography with 3% MeOH in chloroform. Yield, 26%, white solid; mp, 186-88°C; MS (ESI): 552 (M^++Na), 520 (M^++1); analysis: $C_{25}H_{27}N_3O_{10}$, 1.5 H_2O requires C, 53.90; H, 5.39; N, 7.55; found: C, 53.96; H, 5.12; N, 7.33 %.

Example 65a:

(2-Ethoxycarbonylmethoxy-4-formyl-phenoxy)-acetic acid ethyl ester

3,4-Dihydroxy-benzaldehyde was treated with 2-bromo-acetic acid ethyl ester in the presence of K_2CO_3 and processed as described in the synthesis of example 20a. The crude product was purified using flash chromatography (silica gel, 30-50% EtOAc in PE 60-80°C). Yield, 87%; mp, 56°C (EtOAc- PE 60-80°C); MS (EI): 310 (M^+), 237, 163, 149; analysis: $C_{15}H_{18}O_7$, 0.5 H_2O requires C, 56.37; H, 5.95; found: C, 56.72; H, 5.79%.

Example 65b:

(2-Ethoxycarbonylmethoxy-4-hydroxy-phenoxy)-acetic acid ethyl ester

The compound of example 65a obtained above was treated with 3-chlorobenzoic acid in dichloromethane as reported in the literature (I. M. Godfrey et.al, JCS Perkin I, 1974, 1353,). The formyl ester obtained was purified using column chromatography (neutral alumina, 3-5% MeOH in dichloromethane) and crystallized from EtOAc-PE 60-80°C. Yield, 68%; mp, 67°C (EtOAc- PE 60-80°C); MS (EI): 298 (M^+); analysis: $C_{14}H_{18}O_7$ requires C, 56.37; H, 6.08; found: C, 56.12; H, 5.89%.

Example 65c:

(4-Allyloxy-2-ethoxycarbonylmethoxy-phenoxy)-acetic acid ethyl ester

Allyl bromide (25.53 ml; 302 mmol) was added slowly to a mixture of the compound of example 65b (75g; 251.4 mmol), K_2CO_3 (52.04g; 377 mmol) and KI (~1g) in DMF (150 ml) under vigorous stirring for 15 min at room temperature. The reaction mixture was stirred overnight (~16h), treated with water (1lit.), and extracted with EtOAc. The EtOAc layer was washed with water, brine, dried (Na_2SO_4), concentrated and purified using flash chromatography (silica gel, 3% CH_3CN in chloroform) to obtain the title compound as an oil. Yield, 76g (89.7%): MS (EI): 337 (M^+), 136.

Example 65d:

(4-Acetyl-2-ethoxycarbonylmethoxy-5-hydroxy-phenoxy)-acetic acid ethyl ester

The compound of example 65c (38g; 112.5 mmol) was heated with acetyl chloride (9.74ml; 137 mmol) and activated Zn (7.46g) in toluene (250 ml) for 5h

(Synth. Commun. 1998, 28, 2203). to obtain the title compound which was processed as is routinely done and purified using flash chromatography (silica gel, 3% CH_3CN in chloroform). Yield, 30g (78.3%); MS (CI): 409 (M^++29), 381(M^+); analysis: $C_{16}H_{20}O_8$ requires C, 56.47; H, 5.92; found: C, 56.05; H, 5.59%.

Example 65e:

(4-{2-Bromo-acetyl}-2-ethoxycarbonylmethoxy-5-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 65d using the procedure described in example 50b. The crude product was purified using flash chromatography (silica gel, with 3% CH_3CN in chloroform). Yield, 50%; MS (CI): 447 (M^++29), 419 (M^++1); analysis: $C_{16}H_{19}BrO_8$ requires C, 45.84; H, 4.57; Br, 19.06; found: C, 45.45; H, 4.26; Br, 18.91%.

Example 65f:

4-(2-*tert*-Butoxycarbonylamino-acetyl)-2-ethoxycarbonylmethoxy-5-hydroxy-phenoxy]-acetic acid ethyl ester

The title compound was obtained from the compound of example 65e using the procedure described in example 16a (1.5N alcoholic HCl was used instead of 1.5N aqueous HCl). The crude product was purified using flash chromatography (silica gel, 3% CH_3CN in chloroform). Yield, 30%; mp, 73-74°C; MS (ESI^+): 478 (M^++Na), 456 (M^++1); analysis: $C_{21}H_{29}NO_{10}$ requires C, 55.38: H, 6.42; N, 3.06; found: C, 55.69; H, 6.74; N, 3.19%.

Example 65g:

(4-{2-Amino-acetyl}-2-ethoxycarbonylmethoxy-5-hydroxy-phenoxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 65f using the procedure described in example 5b.

Example 65h:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-2-ethoxycarbonyl methoxy-5-hydroxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 65g

using the procedure described in example 1g. The crude product was purified using flash chromatography (silica gel, 10% CH_3CN in chloroform, 1% MeOH in chloroform). Yield, 22%; mp 168-69°C (EtOAc); MS (ESI^+): 519 (M^++23), 497(M^++1); analysis: $C_{25}H_{24}N_2O_9$, $2H_2O$ requires C, 56.34; H, 5.20; N, 5.25; found: C, 56.60; H, 4.86; N, 5.19%.

Example 65i:

(2-Ethoxycarbonylmethoxy-5-hydroxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 65h using the procedure described in example 1h. The crude product was purified using flash chromatography (silica gel, 10% CH_3CN, 1% MeOH in chloroform). Yield, 94%; mp 142-43°C; MS (ESI^+): 553 (M^++Na), 531(M^++1); analysis: $C_{25}H_{26}N_2O_9S$ requires C, 56.60; H, 4.94; N, 5.28; found: C, 56.82; H, 4.71; N, 5.23%.

Example 66:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-piperazine-1-yl)-acetic acid ethyl ester; acetic acid salt

The title compound was obtained from the compound of example 66f by subjecting it to hydrogenation in AcOH and ethanol over 10% Pd-C, using the procedure reported in the literature (see Gante.J. et. al. Bioorg. Med. Chem. 6, 2425, 1996). The title compound was purified using an RP-18 column(40% MeOH in water containing 0.2% AcOH). Yield, 39.5%; mp, 211-12°C; MS (ESI^+): 388 (M^++1), analysis: $C_{21}H_{29}N_5O_6$ requires C, 56.38; H, 6.49; N, 15.66; found: C, 55.57; H, 6.34; N, 15.02%.

Example 66a:

(5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl)-acetic acid ethyl ester

The title compound was obtained from Glycine ethyl ester hydrochloride using the procedure described in example 1g. It was purified using flash chromatography (silica gel, 3.5% CH_3CN in chloroform). Yield 88%; mp, 105°C; MS (EI): 244 (M^+), 170, 114; analysis: $C_{13}H_{12}N_2O_3$ requires: C, 63.93; H, 4.95; N,

11.47; found: C, 63.48; H, 4.54; N, 11.35%.

Example 66b:

(5-{N-Hydroxycarbamimidoyl}-1-oxo-1,3-dihydro-isoindol-2-yl)-acetic acid ethyl ester

A mixture of the compound of example 66a (1.85 g; 8 mmol), hydroxylamine hydrochloride (2.21g; 31.82 mmol) and Na_2CO_3 (1.55g; 14.62 mmol) in methanol (14.3 ml) and water (43 ml) was refluxed in an atmosphere of nitrogen for 3h. It was concentrated and extracted with EtOAc. The organic layer was dried (Na_2SO_4), concentrated and purified by trturation with EtOAc and PE 60-80°C to obtain the title compound. Yield, 1g (47%); mp, 150-51°C; MS (ESI): 286 (M^++Na), analysis: $C_{12}H_{13}N_3O_4$ requires C, 54.75; H, 4.98; N, 15.96; found: C, 54.70; H, 4.92; N, 15.89%.

Example 66C:

(5-{5-Methyl-[1,2,4]oxadiazol-3-yl}-1-oxo-1,3-dihydro-isoindol-2-yl)-acetic acid ethyl ester

The compound of example 66b (1g; 3.8 mmol) in acetic anhydride (20 ml) was heated at 120°C for 4h. It was concentrated and purified using flash chromatography (silica gel, 5% CH_3CN in dichloromethane) to obtain the title compound. Yield, 0.6g (55%); mp, 155°C; MS (ESI^-): 286 (M-1), analysis: $C_{14}H_{13}N_3O_4$ requires C, 58.53; H, 4.56; N, 14.63; found: C, 58.13; H, 4.79; N, 14.14%.

Example 66d:

(5-{5-Methyl-[1,2,4]oxadiazol-3-yl}-1-oxo-1,3-dihydro-isoindol-2-yl)-acetic acid

A solution of the compound of example 66c(0.5g; 1.7 mmol) in methanol (13.6 ml) was stirred with 1N NaOH (3.4 ml; 3.4 mmol) at room temperature for 1h. It was concentrated, treated with water extracted with EtOAc. The aqueous layer was acidified with dil. HCl. The title compound precipitated as a white solid. It was filtered, washed with water and dried. Yield, 0.45g (95%); mp, 230-31°C; MS (ESI^-): 272 (M-1), analysis: $C_{13}H_{11}N_3O_4$ requires C, 51.14; H, 4.06; N, 15.38; found: C, 51.10; H, 4.20; N, 14.90%.

Example 66e:

(4-[2S-(5-Methyl-[1,2,4]oxadiazol-3-yl)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperazin-1-yl)-acetic acid ethyl ester

DCC (0.433g; 2.1 mmol) was added with vigorous stirring to a solution of the compound of example 66d (0.53g; 1.9 mmol) and 1-hydroxybenzotriazole (0.338g; 2.47 mmol) in dry DMF (15 ml) at 0°C. After 10 min. piperazin-1-yl-acetic acid ethyl ester (0.43g; 2.47 mmol) was added to the mixture It was stirred at 0°C for 1h and then kept in the freezer over night. The DCU was filtered off and the filtrate was washed with 1N aqueous $NaHCO_3$, water, 1N aqueous HCl, brine, dried (Na_2SO_4), concentrated and purified using flash chromatography (silica gel, 5% MeOH in chloroform) to obtain the title compound. Yield, 0.64g (77%); mp, 189-90°C; MS (ESI^+): 450 (M^++Na), analysis: $C_{21}H_{25}N_5O_5$ requires C, 59.01; H, 5.90; N, 16.38; found: C, 58.80; H, 5.93; N, 15.80%.

Example 67:

(1-{2S-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-3-(4-hydroxy-phenyl)-propionyl}-piperidin-4-yloxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 67g in two steps, using the procedures sequentially, described in examples 1i and 4. It was purified using flash chromatography (silica gel, 3% MeOH in chloroform). Yield, 48%; mp, 116-18°C; MS (ESI): 547 (M^++Na), 525. (M^++1), analysis: $C_{27}H_{32}N_3O_7$, $1.5H_2O$ requires: C, 58.74; H, 5.80; N, 10.15; found: C, 58.60; H, 5.97; N, 10.00%.

Example 67a:

4-Hydroxy-piperidine-1-carboxylic acid benzyl ester

Benzyl chloroformate (8.55 mL; 60 mmol) was added drop wise over a period of 30 min to a well stirred chilled mixture of piperidin-4-ol (5g; 49.44 mmol), 1N aqueous NaOH (60 mL; 60 mmol) and dioxane (60 mL),. The mixture was stirred for 30 min. at room temperature, treated with water, acidified with conc. HCl to pH 2 and extracted with EtOAc. The EtOAc layer was washed with water, brine, dried (Na_2SO_4), concentrated and purified using flash

chromatography (silica gel, 50% CH_2Cl_2 in PE 60-80°C, 10% CH_3CN + 2% MeOH in chloroform). Yield, 12.5g (99%), oil; MS (CI): 236 (M^++1). 218, 192, 174, 91.

Example 67b:

4-Ethoxycarbonylmethoxy-piperidine-1-carboxylic acid benzyl ester

The compound of example 67a (16g; 70 mmol) in dioxane (25 ml) was added drop wise at 5-10°C to (toluene washed) 55% NaH (3.84g; 80 mmol) suspended in dioxane (25 ml) over a period of 30 min. in an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 1h, cooled to 0°C and treated to a drop wise addition of ethyl 2- bromoacetate (8.9 ml; 80 58 mmol) over a period of 15-20 min. It was poured over crushed ice, and extracted with EtOAc. The EtOAc layer was washed with brine, dried (Na_2SO_4), concentrated and purified using flash chromatography (silica gel, 5-10% CH_3CN in chloroform). Yield, 18.5g (84.55%), oil; MS (ESI): 344 (M^++Na), 322 (M^++1).

Example 67c:

(Piperidin-4-yloxy)-acetic acid ethyl ester, hydrochloride

The compound of example 67b (14g, 43.56 mmol) in MeOH (150 ml) and AcOH (10 ml) was hydrogenated using 10% Pd-C (0.15g) at 40-50 psi for 4h. The catalyst was filtered off and treated with ethereal HCl. It was concentrated and the title compound obtained was crystallized from dry MeOH in ether. Yield, 9.5g (97.5%).

Example 67d:

(1-{2-Benzyloxycarbonylamino-3-[4-benzyloxycarbonyloxy-phenyl]-propionyl}-piperidine-4-yloxy)-acetic acid ethyl ester

DCC (4.12g; 20 mmol) in EtOAc (10 ml) was added under vigorous stirring to a solution of di-Z-L-Tyr (8.08g; 18 mmol) and HOBt (2.7g; 20 mmol) in EtOAc (100 ml) at 0°C. After 10 min, the compound of example 67c (4.46g; 19.93 mmol) was neutralized with Et_3N (2.8 ml; 20 mmol) in DMF (10 ml) at 0°C and was added to the reaction mixture. The resulting mixture was stirred at 0°C for 2h and then kept in the freeze over night (~16h). DCU was filtered off. The filtrate was successively washed with 1N $NaHCO_3$, water, 1N HCl and brine. It was dried

over anhydrous Na_2SO_4. The solvent was removed. The crude product was purified by flash chromatography with 10% CH_3CN in $CHCl_3$. Yield, 8.2g (73.6%); MS (ESI): 641 (M^++Na), 619 (M^++1); analysis: $C_{34}H_{38}N_2O_9$ requires: C, 66.01; H, 6.19; N, 4.53; found: C, 66.39; H, 6.58; N, 4.81%.

Example 67e:

(1-{2-Amino-3-[4-hydroxy-phenyl]-propionyl}-piperidin-4-yloxy)-acetic acid ethyl ester, hydrochloride

The compound of example 67d in MeOH and AcOH was hydrogenated using 10% Pd-C for 2h at 40-50 psi. The catalyst was filtered off and ethereal HCl added. It was concentrated and the title compound obtained was crystallized from dry MeOH in ether. Yield, 85%; MS (ESI): 373 (M^++Na), 351 (M^++1).

Example 67f:

(1-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-3-(4-hydroxy-phenyl)-propionyl}-piperidin-4-yloxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 67e using the procedure described in example 1g. It was purified using flash chromatography (silica gel, 10% CH_3CN, 2% MeOH in $CHCl_3$). Yield, 22%; mp, 73-75°C; MS (CI): 520 (M^++29), 492. (M^++1), 292, 188, 158; analysis: $C_{27}H_{29}N_3O_6$ requires: C, 65.98; H, 5.95; N, 8.55; found: C, 65.68; H, 5.94; N, 8.18%.

Example 67g:

(1-{3-[4-Hydroxy-phenyl]-2-(1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl)-propionyl}-piperidin-4-yloxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 67f using the procedure described in example 1h. It was purified using flash chromatography (silica gel. 10% CH_3CN and 1% MeOH in chloroform). Yield, 95%; mp, 110°C; MS (ESI): 548 (M^++Na), 526. (M^++1). 292, 188. 158.

Example 68:

(1-{2-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-piperidin-4-yloxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 68d in two steps, using the procedures sequentially, described in examples 1i and 4. It was purified using flash chromatography (silica gel, 25% CH_3CN in chloroform, 2-5% MeOH in chloroform). Yield, 67%, white solid; mp, 204-06°C (MeOH: $CHCl_3$-PE 60-80°C); MS (ESI): 441 (M^++Na), 419 (M^++1); analysis: $C_{20}H_{26}N_4O_6$ requires: C, 57.41; H, 6.26; N, 13.39; found: C, 57.51; H, 6.60; N, 13.49%.

Example 68a:

(1-{2-*tert*-Butoxycarbonylamino-acetyl}-piperidin-4-yloxy)-acetic acid ethyl ester

The title compound was obtained by reaction of *tert*-butoxycarbonylamino-acetic acid and Piperidin-4-yloxy)-acetic acid ethyl ester, hydrochloride (67c), using mixed anhydride procedure described for compound in example 25a. The crude product was purified by flash chromatography with 1% MeOH in chloroform. Yield, 84.6%, oil; analysis: $C_{16}H_{28}N_2O_6$ requires: C, 55.80; H, 8.19; N, 8.13; found: C, 55.48; H, 8.28; N, 8.06%.

Example 68b:

(1-{2-Amino-acetyl}-piperidin-4-yloxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 68a using the procedure described in example 5b. Yield, 98%; MS (ESI): 267 (M^++Na), 245 (M^++1).

Example 68c:

(1-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-piperidin-4-yloxy) - acetic acid ethyl ester

The title compound was obtained from the compound of example 68b using the procedure described in example 1g. It was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform, 2-5% MeOH in chloroform). Yield, 38.6%; mp, 109-11°C; MS (ESI): 408 (M^++Na), 386 (M^++1); analysis: $C_{20}H_{23}N_3O_5$ requires: C, 62.33; H, 6.01; N, 10.90; found: C, 62.74; H, 6.19; N, 10.99%.

Alternative method for example 68c:

(5-cyano-1-oxo-1,3-dihydro-isoindol-2-yl)-acetic acid: Compound of

example 66a (3.0g; 12.8 mmol) was dissolved in THF (47.3 ml) and hydrolyzed with 0.5M LiOH (27.7 ml) for 30 min. The pH of the reaction was brought to 2 by adding 1N HCl. Most of the organic solvent was removed. The solid was filtered and washed with water. After drying under vacuum for 2h at 50°C it was crystallized from hot EtOAc-PE 60-80°C. Yield, 2.56g (91.8%); mp, 262°C; MS (EI): 216 (M^+), 171, 115; analysis: $C_{11}H_8N_2O_3$ $0.25H_2O$ requires: C, 59.81; H, 3.86; N, 12.71; found: C, 60.17; H, 3.67; N, 13.06%.

(5-cyano-1-oxo-1,3-dihydro-isoindol-2-yl)-acetic acid: obtained above was reacted with (Piperidin-4-yloxy)-acetic acid ethyl ester, hydrochloride (67c) by mixed anhydride method as described for the preparation of 25a to obtain 68c in 60% yield.

Example 68d:

(1-{2-[1-Oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-piperidin-4-yloxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 68c using the procedure described in example 1h. It was purified using flash chromatography (silica gel, 25% CH_3CN in chloroform). Yield, 81%, yellow solid; mp, 177-80°C ($CHCl_3$- PE 60-80°C); MS (ESI): 442 (M^++Na), 420 (M^++1); analysis: $C_{20}H_{25}N_3O_5S$ requires: C, 57.26; H, 6.01; N, 10.02; S, 7.64; found: C, 57.44; H, 6.24; N, 10.27; S, 7.96%.

Example 69:

(1-{3-[5-(N-Hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-propionyl}-piperidin-4-yloxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 69d in two steps, using the procedures sequentially, described in examples 1i and 4. It was purified using flash chromatography (silica gel, 25% CH_3CN in chloroform, by 2-5% MeOH in chloroform). Yield. 44%, white solid; mp, 151-52°C; MS (ESI): 455 (M^++Na), 433 (M^++1); analysis: $C_{21}H_{28}N_4O_6$, requires: C, 58.32; H, 6.53; N, 12.95; found: C, 57.92; H, 6.61; N, 12.89%.

Example 69a:

(1-{3-*tert*-Butoxycarbonylamino-propionyl}-piperidin-4-yloxy)-acetic acid ethyl ester

Treatment of Boc-β–Ala with (Piperidin-4-yloxy)-acetic acid ethyl ester, hydrochloride (67c), by mixed anhydride procedure described for compound in example 25a.The crude product was purified by flash chromatography with 1% MeOH in chloroform. Yield, 70%, oil; MS (CI): 387 (M^++29), 359 (M^++1), 259 (100%); analysis: $C_{17}H_{30}N_2O_6$ requires: C, 56.97; H, 8.44; N, 7.82; found: C, 56.67; H, 8.56; N, 7.60%.

Example 69b:

(1-{3-Amino-propionyl}-piperidin-4-yloxy)-acetic acid ethyl ester, hydrochloride

The title compound was obtained from the compound of example 69a using the procedure described in example 5b; Yield, 98%; mp, 70°C; MS (ESI): 259 (M^++1); analysis: $C_{12}H_{23}ClN_2O_4$ requires: C, 48.90; H, 7.86; N, 9.50; Cl, 12.03; found: C, 48.93; H, 8.18; N, 9.61; Cl, 11.83%.

Example 69c:

(1-{3-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-propionyl}-piperidine-4-yl oxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 69b using the procedure described in example 1g. It was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform, 2-5% MeOH in chloroform). Yield, 35%; mp, 60°C; MS (ESI): 422 (M^++Na), 400 (M^++1); analysis: $C_{21}H_{25}N_3O_5$, 0.5 H_2O requires: C, 61.69; H, 6.12; N, 10.28; found: C, 62.06; H, 6.17; N, 10.62%.

Example 69d:

(1-{3-[1-Oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-propionyl}-piperidin-4-yloxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 69c using the procedure described in example 1h. It was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform, 1% MeOH in chloroform).

Yield, 98%, yellow solid; mp, 190°C; MS (ESI): 456 (M^++Na), 434 (M^++1); analysis: $C_{21}H_{27}N_3O_5S$ requires: C, 58.18; H, 6.28; N, 7.69; S, 7.4; found: C, 58.61; H, 6.60; N, 9.76; S, 7.29%.

Example 70:
(1-{2-[5-(5-Methyl-isoxazol-3-yl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-piperidin-4-yloxy)-acetic acid ethyl ester

A solution of the compound of example 68 (1.3g; 3.1 mmol) in acetic anhydride (22 ml) was heated at 120-30°C, following the reported procedure (J. Gante. et. al. Bioorg Med Chem Lett. 1995, 6, 2425). It was purified using flash chromatography (silica gel, 2% MeOH in $CHCl_3$) and crystallized from chloroform-ether to obtain the title compound as a white solid. Yield, 0.96g (69%); mp, 126-27°C; MS (ESI): 443 (M^++1); analysis: $C_{22}H_{26}N_4O_6$, requires: C, 59.72; H, 5.92; N, 12.66; found: C, 59.18; H, 5.90; N, 12.30%.

Example 71:
(1-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-piperidin-4-yloxy)-acetic acid ethyl ester, acetic acid salt, sesquihydrate

The title compound was obtained from the compound of example 69d in two steps, using the procedures sequentially, described in examples 1i and 3. It was purified using, flash chromatography (RP-18 using 30% MeOH and 0.2% AcOH in water) and triturated with MeOH-ether to obtain a white solid. Yield, 42%; mp, 189-90°C; MS (ESI): 403 (M^++1); analysis: $C_{22}H_{30}N_4O_7$, 1.5 H_2O requires: C, 53.93; H, 6.74; N, 11.44; found: C, 53.73; H, 6.58; N, 11.67%.

Example 72:
(1-{2-[5-(*tert*-Butoxycarbonylamino-imino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-piperidin-4-yloxy)-acetic acid ethyl ester, sesquihydrate

$NaHCO_3$ (0.326g; 3.88 mmol) was added at 0°C to a mixture of the compound of example 71 (1.2g; 2.59 mmol), dioxane (15 ml), water (7.5 ml) and 1N aqueous NaOH (2.59 ml). Subsequently di-*tert*-butyl-dicarbonate (0.847g;

3.88 mmol) in dioxane (2ml) was added. The reaction mixture was stirred at room temperature for 1h, stripped off dioxane and extracted with EtOAc. The EtOAc layer was washed with water, dried (Na_2SO_4), concentrated and purified using flash chromatography (silica gel, 25% CH_3CN in chloroform, 2% MeOH in chloroform) to afford the title compound Yield, 0.75g, white solid, (57%); mp, 83-85°C; MS (ESI): 503 (M^++1); analysis: $C_{25}H_{34}N_4O_7$,1.5 H_2O requires: C, 56.65; H, 6.99; N, 10.60; found: C, 56.52; H, 6.87; N, 11.29%.

Example 73:

(1-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-piperidin-4-yloxy)-acetic acid, hydrochloride, trihydrate

Aqueous 1N NaOH (1.81 ml; 1.81 mmol) was added to a well-stirred solution of the compound of example 72 (0.7g; 1.39 mmol) in MeOH (7.2 ml) at room temperature. The reaction mixture was allowed to further stir at room temperature for 1h. Methanol was removed under reduced and the aqueous layer was acidified with dil HCl at 0°C. The reaction mixture was evaporated to dryness. The crude material obtained was dissolved in a solution of 5% MeOH in chloroform (30 ml) and filtered. The filtrate was taken to dryness and the residue was triturated with dry ether to afford the title compound as a pure white solid. Yield, 14%, white solid; mp, 135-36°C; MS (ESI): 373 (M^+-1); analysis: $C_{18}H_{23}ClN_4O_5$, $3H_2O$ requires: C, 46.50; H, 6.29; Cl, 7.63; N, 12.05; found: C, 46.63; H, 6.23; Cl, 7.43; N, 11.64%.

Example 74:

(4-{2-[5-Acetimidoylamino-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-phenoxy)-acetic acid ethyl ester; hydro iodide, hemi hydrate

The title compound was prepared by refluxing a mixture of 74b, 74c and $NaHCO_3$ in acetonitrile for 4h. It was concentrated and purified using flash chromatography (silica gel, 10% CH_3CN and 3% MeOH in chloroform) and triturated with MeOH-ether containing a few drops of EtOAc to obtain a pure white solid. Yield, 26%; mp, 196-97°C; MS (ESI): 426 (M^++1); analysis:

$C_{22}H_{24}IN_3O_6$, 0.5 H_2O, requires: C, 46.94; H, 4.95; N, 7.47; found: C, 46.56; H, 4.54; N, 7.32%.

Example 74a:

(3-Hydroxy-4-{2-[5-nitro-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 41d and ethyl 2-bromomethyl-4-nitrobenzoate using the procedure described in example 1g. It was purified using flash chromatography (silica gel, 5% CH_3CN in chloroform) and crystallized from $CHCl_3$-EtOAc- PE 60-80°C. Yield, 16%, off white solid; mp, 224-26°C; MS (ESI): 437 (M^++Na), 415 (M^++1); analysis: $C_{20}H_{18}N_2O_8$ requires: C, 57.97; H, 4.38; N, 6.76; found: C, 58.23; H, 4.38; N, 6.64%.

Example 74b:

(4-{2-[5-Amino-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-phenoxy)-acetic acid ethyl ester

A mixture of the compound of example 74a, cobalt (II) chloride and Zn powder in DMF and water was stirred to obtain the title compound, according to reported procedure (see Ind. J. Chem. 33B, 758, 1994). It was purified using flash chromatography (silica gel, 10% CH_3CN and 0.5% MeOH in chloroform) and crystallized using $CHCl_3$- PE 60-80°C. Yield, 43%, white solid; mp, 193-94°C; MS (ESI): 407 (M^++Na), 385 (M^++1); analysis: $C_{20}H_{20}N_2O_6$ requires: C, 62.49; H, 5.24; N, 7.29; found: C, 62.95; H, 5.42; N, 7.31%.

Example 74c:

Thioacetimidic acid methyl ester hydroiodide

The title compound was obtained from thioacetamide using the procedure described in example 1i as a white solid white solid. Yield, 72%; mp, 158-60°C; MS (EI): 89 (M^+); ^{1}H NMR (DMSO-D_6): 2.56 (3H, s, CH_3), 2.71 (3H, s, SCH_3), 11.6 (1H, br, NH).

Example 75:

(3-Ethoxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 75c using the procedure described in example 4. It was purified using flash chromatography (silica gel, 2% MeOH in chloroform). Yield, 50%, white solid; mp, 192-94°C; MS (ESI$^-$): 478.55 (M^++Na), 456.37 (M^++1); analysis: $C_{23}H_{25}N_3O_7$, requires C, 60.65; H, 5.53; N, 9.23; found: C, 60.57; H, 5.42; N, 8.73%.

Example 75a:

(4-{2-[5-Cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-ethoxy-phenoxy)-acetic acid ethyl ester

Ethyl bromide (0.662 ml; 8.87 mmol) was added to a mixture of the compound of example 41f (0.7g; 1.77 mmol), anhydrous K_2CO_3 (1.23g; 8.87 mmol) and KF (0.07g) in DMF (60 ml), with stirring at room temperature. The reaction mixture was stirred at room temperature for 16h, poured over ice containing dill. HCl and extracted with EtOAc. The EtOAc layer was washed with water, dried (Na_2SO_4.), concentrated and purified using flash chromatography (silica gel, 5% CH_3CN in chloroform). Yield, 0.585g (78%); white solid; mp, 180-81°C ($CHCl_3$- PE 60-80°C); MS (ESI): 445 (M^++Na), 423 (M^++1); analysis: $C_{23}H_{22}N_2O_6$, requires C, 65.40; H, 5.25; N, 6.63; found: C, 65.75; H, 5.07; N, 6.11%.

Example 75b:

(3-Ethoxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 75a using the procedure described in example 1h. It was purified using flash chromatography (silica gel, 2% MeOH in chloroform). Yield, 95%, yellow solid; mp, 176-77°C; MS (ESI): 480 (M^++Na), 458 (M^++1); analysis: $C_{23}H_{24}N_2O_6S$, requires C, 60.51; H, 5.30; N, 6.14; S, 7.02; found: C, 60.17; H, 5.36; N, 5.66; S, 7.39%.

Example 75c:

(3-Ethoxy-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 75b using the

procedure described in example 1i. Yield, 98%, yellow solid; mp, 169-72°C; MS (ESI): 471.5 (M^++1),

Example 76:

(4-{2-[5-carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-ethoxy-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 75c using the procedure described in example 1. It was purified using flash chromatography (RP-18 with 40% MeOH and 2% AcOH in water) and crystallized using MeOH-ether. Yield, 0.44g (59%); mp, 202-03°C; MS (ESI^+): 440.54 (M^++1); analysis: $C_{25}H_{29}N_3O_8$, requires C, 60.11; H, 5.85; N, 8.41; found: C, 59.87; H, 5.87; N, 8.33%.

Example 77:

(4-{2-[5-Carbamimdoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-ethoxy-phenoxy)-acetic acid, hydrochloride, hemihydrate

Aqueous 1N NaOH (1.6 ml; 1.6 mmol) was added to a well stirred mixture of the compound of example 76 (0.4g; 0.8 mmol) and $NaHCO_3$ (0.1g; 1.2 mmol) in dioxane-water (1:1; 5 ml) at 0°C. Subsequently di-*tert*-butyldicarbonate (0.262g; 1.2 mmol) in dioxane (2.5 ml) was added. The reaction mixture was gradually brought to room temperature, and then allowed to stir for another 1h. Dioxane was removed under reduced pressure. The residue was treated with water and extracted with EtOAc. The aqueous layer was acidified with 6N HCl to pH 3 and kept at room temperature for 16h. The white solid that separated was filtered, washed with water, MeOH, ethyl acetate and dried to afford the pure title compound. Yield, 0.126g (35%); mp, 241-42°C; MS (ESI^+): 413.61 (M^++1); analysis: $C_{21}H_{22}ClN_3O_6$, 0.5 H_2O; requires C, 55.16; H, 5.03; N, 9.19; found: C, 55.16; H, 5.43; N, 9.22%.

Example 78:

(3-Hydroxy-4-{2-[1-oxo-5-(5-oxo-2,5-dihydro-[1,2,4]oxadiazol-3-yl)-1,3-

dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

A mixture of the compound of example 42 (0.3g; 0.7 mmol) and 1,1'-carbonyldiimidazol (0.17g; 1.05 mmol) in DMF (10 ml) was stirred at room temperature for 12h. The reaction mixture was diluted with water (100 ml) and extracted with EtOAc. The EtOAc layer was washed with 1N HCl, water, brine, dried (Na_2SO_4), concentrated, purified using flash chromatography (silica gel, 5% MeOH in chloroform) and crystallized from MeOH-ether to obtain the title compound. Yield, 0.032g; (10%), white solid; mp, 223-25°C; MS (ESI^-): 452.59 (M-1), analysis: $C_{22}H_{19}N_3O_8$, requires C, 57.09; H, 4.32; N, 9.08; found: C, 57.74; H, 4.18; N, 8.93%.

Example 79:
(4-{2-[5-(Acetylamino-imino-methyl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-phenoxy)-acetic acid ethyl ester

A mixture of the compound of example 42 (0.5g; 1.17 mmol), KF (0.05g), pyridine (0.189 ml; 2.34 mmol) and acetyl chloride (0.167 ml; 2.34 mmol) in DMF (10 ml) was stirred at room temperature for 3h. The reaction mixture was diluted with ice water (100 ml) and extracted with dichloromethane. The organic layer was washed with water, brine, dried, (Na_2SO_4) and concentrated to obtain the crude product, which was purified by triturating with MeOH, $CHCl_3$ and ether to obtain the title compound as a pure white solid. Yield, 0.414g; (75%); mp, 196-98°C; MS (ESI^+): 470.61 (M^++1), analysis: $C_{23}H_{23}N_3O_8$, requires C, 58.85; H, 4.94; N, 8.95; found: C, 58.47; H, 4.44; N, 8.48%.

Example 80:
(3-Acetoxy-4-{2-[5-(5-methyl-[1,2,4]oxadiazol-3-yl)-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 42 using the procedure described in example 79 with the exception of using 8 equivalent of acetyl chloride and three times the amount of KF used earlier. Yield, 26%; mp, 162-64°C; MS (ESI^+): 494 (M^++1); analysis: $C_{25}H_{23}N_3O_8$, requires C, 59.70; H,

4.78; N, 8.36; found: C, 60.08; H, 4.11; N, 7.85%.

Example 81:

(4-{2-[5-Carbamimidoyl-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-3-hydroxy-2-propyl-phenoxy)-acetic acid ethyl ester, acetic acid salt, hemi hydrate

A mixture of the compound of example 58 (0.15g; 0.319 mmol), glacial acetic acid (20 ml) and Ac_2O (0.066 ml; 0.703 mmol) was stirred at room temperature for 10 min. The mixture was filtered and the filtrate was hydrogenated using 10% Pd-C (0.02g) at 20 psi for 15 min. The catalyst was filtered off and the filtrate was evaporated to dryness. The crude product was purified using flash chromatography (silica gel, 40 % MeOH and 0.2% AcOH in water). The pure product was crystallized using MeOH-ether. Yield, 0.105g (64%); mp, 186-88°C; analysis: $C_{26}H_{31}N_3O_8$ 0.5 H_2O, requires C, 59.71; H, 6.12; N, 8.04; found: C, 59.53; H, 5.94; N, 7.45%.

Example 82:

(3-Hydroxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-2-propyl-phenoxy)-acetic acid, sesquihydrate

NaOH (0.038 g; 0.937 mmol) in absolute EtOH (1 ml) was added to a suspension of the compound of example 58 (0.1g; 0.0.213 mmol) in absolute EtOH (5 ml), and the clear solution was stirred at room temperature till the starting material was consumed. It was concentrated treated dil. HCl. and evaporated to dryness. The crude material was purified using flash chromatography (RP-18 with 1:1 MeOH: 0.2% AcOH in water). Triturating with ether and a trace amount of methanol purified the residue. Yield, 0.35g (37%), white solid; analysis: $C_{22}H_{23}N_3O_7$ 1.5 H_2O, requires C, 56.35; H, 5.55; N, 8.97; found: C, 56.77; H, 4.98; N, 8.92%.

Example 83:

(3-Allyloxy-4-{2-[5-(N-hydroxycarbamimidoyl)-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hemihydrate

The title compound was obtained from the compound of example 83c using the procedure described in example 4. It was purified using flash chromatography (silica gel, 4% CH_3CN in chloroform, 2% MeOH in chloroform). Yield, 77%, white solid; mp, 182-83°C; analysis: $C_{24}H_{25}N_3O_7$, 0.5 H_2O, requires C, 60.49; H, 5.46; N, 8.81; found: C, 60.22; H, 5.09; N, 8.59%.

Example 83a:

(3-Allyloxy-4-{2-[5-cyano-1-oxo-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester

The title compound was obtained from the compound of example 41f using the procedure described in example 75a. It was purified using flash chromatography (silica gel, 5-10% CH_3CN in chloroform). Yield, 76%, white solid; mp, 126-28°C ($CHCl_3$-PE 60-80°C); MS (ESI): 457.523(M^++Na), 435.5 (M^++1); analysis: $C_{24}H_{22}N_2O_6$, requires C, 66.35; H, 5.10; N, 6.45; found: C, 66.14; H, 5.81; N, 6.97%.

Example 83b:

(3-Allyloxy-4-{2-[1-oxo-5-thiocarbamoyl-1,3-dihydro-isoindol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hemihydrate

The title compound was obtained from the compound of example 83a using the procedure described in example 1h. It was purified by flash chromatography (silica gel, 5% CH_3CN in chloroform, 2% MeOH in chloroform). Yield, 76%, yellow solid; mp, 74-76°C; analysis: $C_{24}H_{24}N_2O_6S$, 0.5 H_2O, requires C, 60.31; H, 5.24; N, 5.86; S, 6.70; found: C, 60.58; H, 4.97; N, 5.83; S, 7.03%.

Example 83c:

(3-Allyloxy-4-{2-[5-methylsulfanylcarbonimidoyl-1-oxo-1,3-dihydro-iso indol-2-yl]-acetyl}-phenoxy)-acetic acid ethyl ester, hydroiodide

The title compound was obtained from the compound of example 83b using the procedure described in example 1i. Yield, 98%, yellow solid; mp, 130°C (d); MS (CI): 512 (M^++29), 484 (M^++1); analysis: $C_{25}H_{27}IN_2O_6S$, requires C, 49.29; H, 4.15; N, 4.02; I, 20.18; S, 5.38; found: C, 49.19; H, 4.46; N, 4.49; I, 20.49; S, 5.25%.

The efficacy of the present compounds in antagonizing the activity of the fibrinogen receptor can be determined by a number of pharmacological assays well known in the art, such as described below. The exemplified pharmacological assays, which follow herein below, have been carried out with the compounds of the present invention and their salts.

In vitro Biological Experiments

Human blood (150 ml) was collected from the ante-cubital vein of normal healthy volunteers (who were not on any medication for the past two weeks), into a siliconized glass bottle containing 25 ml of acid-citrate-dextrose (ACD) solution and 10 units of hirudin. The blood was immediately centrifuged at 200 X g for 20 min at room temperature. Platelet-rich plasma (PRP) was separated and the platelet count read using a Beckman Coulter A^{c}T diff Counter. The tubes were centrifuged again at 2000 X g for 10 min at room temperature, to get platelet-free plasma (PFP). The platelet count of PRP was adjusted to 3 X 10^8 platelets/ml by appropriate dilution with PFP. All *in vitro* experiments were conducted using PRP with adjusted number of platelets.

Inhibition of platelet aggregation in human PRP (Born, G. V. R.; Cross, M. J., J. Physiol, 1963, 168, 175)

PRP was incubated with different concentrations of the test compound for 3 min at 37°C. Platelet aggregation was then induced by the addition of ADP (5-15μM final concentration). Percent inhibition of platelet aggregation was then calculated by comparing test aggregation values with control values.

Inhibition of aggregation of gel-filtered platelets (GFP) (Charo, I. F., Nanizzi, L. *et al*, J. Biol. Chem, 1991, 266, 1415-1421)

PRP was centrifuged at 285 X g for 20 min to pellet the platelets. The platelet pellet was resuspended in Tyrode's buffer containing hirudin (0.06 unit/ml) and apyrase (40 mcg/ml). The platelet suspension was layered on to a Sepharose 2B (Sigma) column, previously equilibrated with Tyrode buffer (pH 7.4). Elution of platelets was carried out with Tyrode buffer containing dextrose (5.5 mM) and BSA (0.35%). The count of GFP was adjusted to 3 X 10^8 platelets/ml with Tyrode's buffer. GFP suspension was mixed with ADP and fibrinogen and aggregation of platelets was studied in presence and in absence of the test compound. Similarly, the effect of the test compound on thrombin-induced platelet aggregation was studied.

Receptor Binding assay (Mousa S. A., et al. Cardiology. 1993: 83: 374 - 382. and Charo, I. F., Nanizzi, L. *et al* , J. Biol. Chem., 1991, 266, 1415-1421)

Biotinylation of Fibrinogen

Fibrinogen was dialyzed against 0.1 M $NaHCO_3$, 0.1 M NaCl, pH 8.2 and spun in an ultracentrifuge at 1,00000 X g for 30 minutes at 4°C to remove any particulate matter. The protein concentration was adjusted to 1 mg/ml. Solid sulfo-N-hydroxy-succinimido-biotin (0.2 mg of biotin ester/ml of adhesive protein) was added and gently mixed end-over-end for 30 minutes at room temperature. The unreacted biotin ester was removed by exhaustive dialysis against 50 mM Tris.HCl, 100 mM NaCl, 0.05% NaN_3, pH - 7.4 at 4°C. The biotinylated fibrinogen is stored at 4°C until use.

Method

The GP IIb/IIIa protein (1 mg/ml) was diluted 1:200 with a Triton X-100-free buffer containing 20mM Tris-HCl, 150 mM NaCl, 1 mM $CaCl_2$, 0.02% NaN_3 (Buffer A). This protein was immediately added to 96-well microtiter plates (Immulon II - Dynatech) at 0.1 ml (0.5 mg) per well and incubated overnight at 4°C. The wells were washed once with 50 mM Tris, 100 mM NaCl, 2 mM $CaCl_2$, 0.02% NaN_3, pH 7.4 (buffer B). The unbound sites were then blocked by incubating the wells with

0.1 ml solution buffer B containing 35 mg/ml BSA, for 2 hours at 30°C. The wells were washed again with buffer B containing 1 mg/ml BSA (incubation buffer). The fibrinogen receptor antagonists were added simultaneously with biotinylated fibrinogen, so as to induce competition for binding to the gpIIb/IIIa receptor. Biotinylated fibrinogen (0.1ml/well) was added at a final concentration of 10 nM and incubated for 3 hours at 30°C. After incubation, the wells were aspirated completely and washed once with 250 µl of binding buffer. Bound fibrinogen was quantitated by addition of 0.1 ml of Streptavidin horseradish peroxidase (1:2000 dilution). The wells were then washed with incubation buffer and 100 µl of the substrate 3,3',5,5'-tetramethyl-benzidine dihydrochloride was added. (The substrate was prepared daily following the manufacturer's instructions - 1 mg/ml of substrate prepared in DMSO was added to 9 ml of citrate buffer, pH = 4). The kinetics of colour development was followed at 450 nm (Ref filter - 630 nm) using a microtiter plate reader.

ex vivo Biological Experiments

Mouse *ex vivo* Studies : (Weller, T., Alig, L., *et al* J. Med. Chem., 1996, 39, 3139-3147)

Mice of either sex weighing between 25-35 g were orally fed the test compound. Blood was collected, from the abdominal aorta into ACD solution, at different time-points ranging from 15 min to 6 h. The blood samples were centrifuged at 2000 X g for 10 min to get PFP. This plasma was separated and used as test sample to study its effect on ADP-induced human platelet aggregation.

Guinea Pig *ex vivo* Studies :

Guinea pigs of either sex weighing between 500-800 g were orally fed the test compound. Blood was collected, from the carotid artery into ACD solution, at

different time-points ranging from 1 to 24 h. PRP was separated and the platelet count adjusted to 3 X 10^8 platelets/ml using PFP. The effect of the test compound on ADP-induced guinea pig platelet aggregation was studied.

In vivo Biological Experiments

Thrombocytopenia in Guinea Pigs : (Voelkl K-P., Dierichs, R. Thromb. Res. 1986, 42, 11-20)

Guinea pigs weighing between 500-800 g were orally fed the test compound. After a fixed time interval the guinea pigs were anaethesized and the carotid artery and jugular vein were cannulated. Blood samples were collected from the carotid artery. After collection of the control blood sample (0 min), collagenase (10 mg/kg) was administered through the jugular vein. The endothelium gets damaged by the action of collagenase and causes platelets to aggregate at this site, thereby inducing thrombocytopenia. At every minute thereafter till 10 min and at 15, 20, 25 and 30 min after the administration of collagenase, blood samples were collected. The platelet count was read using the Beckman Coulter A^{c}T diff Counter. All counts were compared with the 0 min (before administration of proaggregatory challenge) sample to determine the fall in the number of free circulating platelets. A graph of the number of platelets against time was plotted and the Area Under the Curve (AUC) was calculated for each animal. Percent protection was determined by comparing the AUCs of treated to control animals.

Thrombus formation in Hamster:

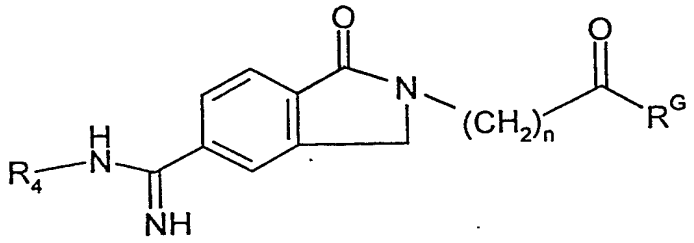
Hamsters weighing between 150-180 g were orally fed the test compound. After a fixed time interval they were anaesthetized and the abdominal aorta exposed. A copper wire with a one-centimeter long coil was inserted through the abdominal aorta, all the way up to the thoracic aorta. After 10 min the copper wire was withdrawn and the size of the thrombus, formed on the wire, determined by estimating the protein content. Percent inhibition of thrombus formation was

determined by comparing the thrombi formed in the drug-treated group with those in the control group.

The compounds of the present invention have an IC_{50} below 100nM, for ADP-induced human platelet aggregation and ~200 pM for fibrinogen binding. Efficacy studies in guinea pigs revealed that the compounds show a long duration of action. The compounds of the present invention also inhibited collagenase-induced thrombocytopenia in guinea pigs. Toxicity studies with some of these molecules revealed that the LD50 was >1000 mg/kg, p.o., in mice and rats. They did not significantly increase the bleeding time in guinea pigs.

We Claim

1. A compound of the general formula (Ih), or a prodrug, tautomeric form, stereoisomer, pharmaceutically acceptable salt, pharmaceutically acceptable solvate or polymorph thereof



(Ih)

wherein

R^G is phenyl, piperidinyl or piperazinyl, substituted with:

(c) at least one substituent selected from: $-CH_2C(O)R^{25}$ and $-T-(CH_2)q-CH_2-C(O)R^{25}$, wherein T is CH_2, O, S or NH, q is 0, 1, 2 or 3; R^{25} is, in each group, selected from: OR^5 and NR^5R^6, wherein R^5 and R^6, which are independent of each other and can be the same or different, are selected from: H, C_1-C_6-alkyl and phenyl; and, optionally,

(d) at least one substituent selected from: -OH, $-NH-C(O)CH_3$ and C_1-C_6-alkyl;

R_4 is selected from: H, OH, -C(O)OH or $-C(O)OC$ C_1-C_6-alkyl; and

n is 1 or 2;

including racemic, R and S configurations of the compound, as well as geometrical E/Z or syn/anti isomers, arising from any asymmetric center in the compound.

Dated this 8th day of October, 2003

Swati Bal-Tembe

Dr. Swati Bal-Tembe
General Manager, Head of Patents and Information
Nicholas Piramal India Limited
Applicant

Abstract

Fibrinogen Receptor Antagonists and their Use

This invention relates to novel bicyclic compounds which are useful as antagonists of the platelet glycoprotein IIb/IIIa fibrinogen receptor complex, to pharmaceutical compositions containing such compounds, processes for preparing such compounds, and to methods of using these compounds, alone or in combination with other therapeutic agents, for the inhibition of platelet aggregation, and for the treatment of thrombotic diseases and other diseases.

To
The Controller of Patents
The Patent Office
At Mumbai

Figure A

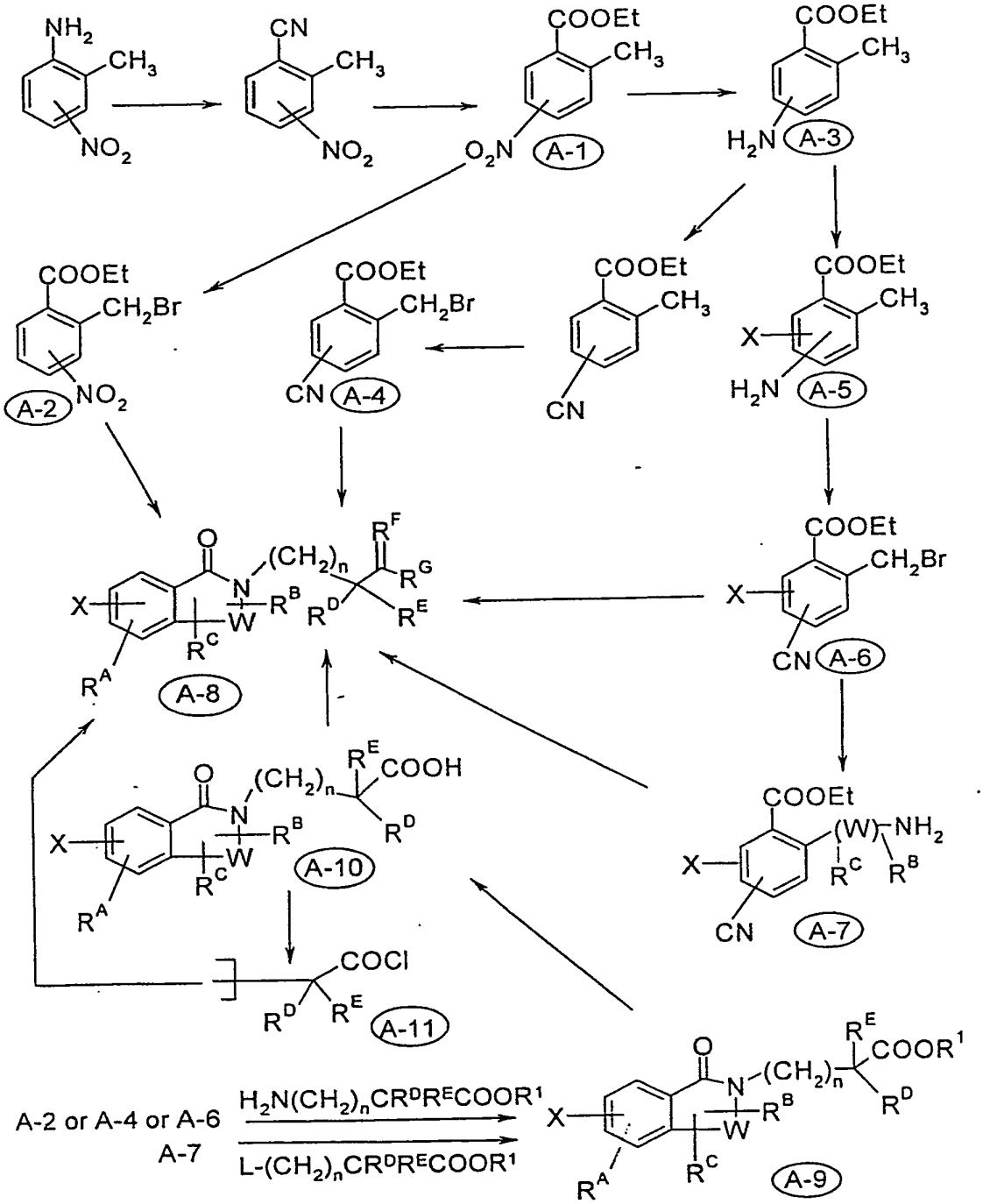


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Figure B

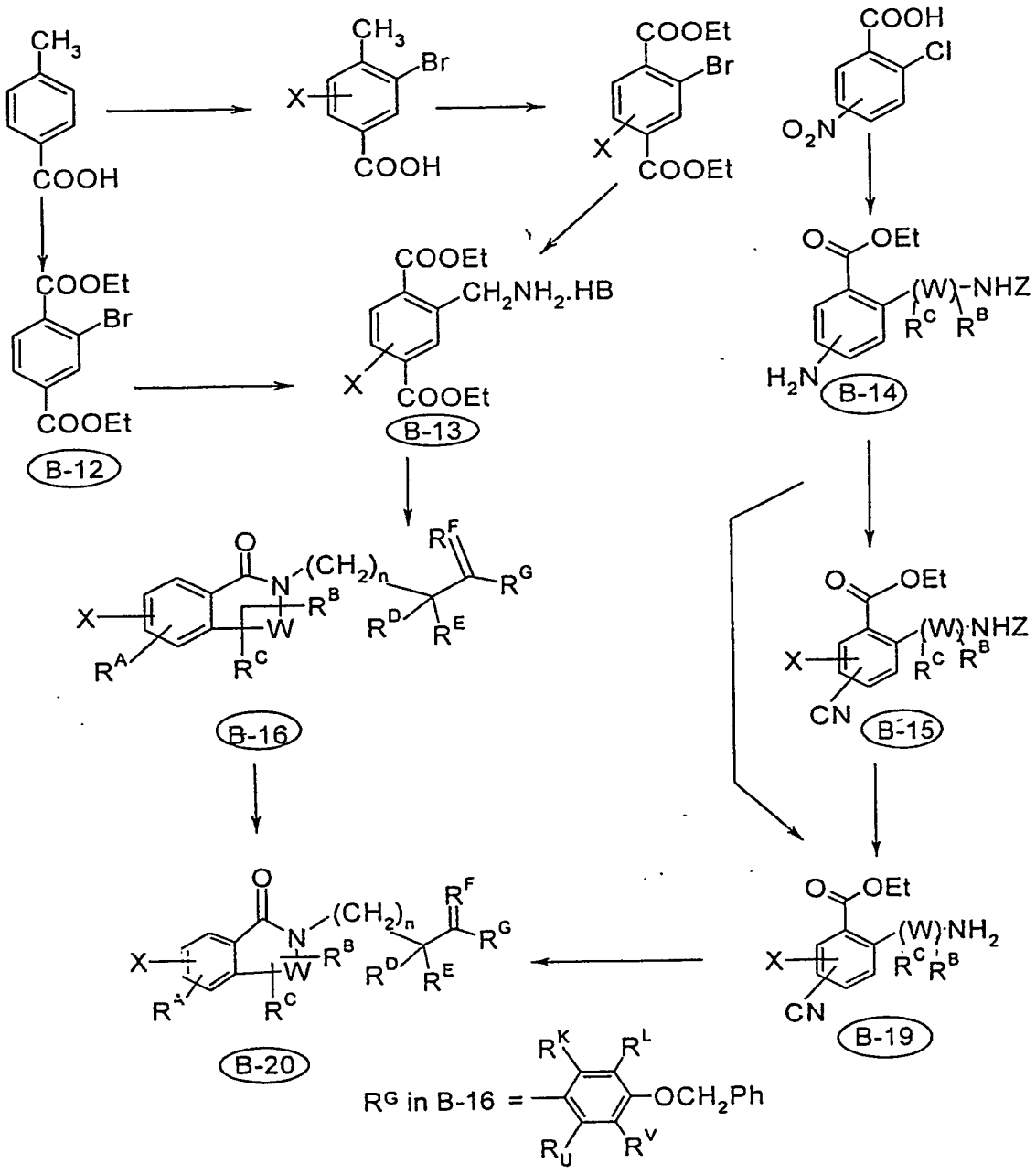

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Figure C

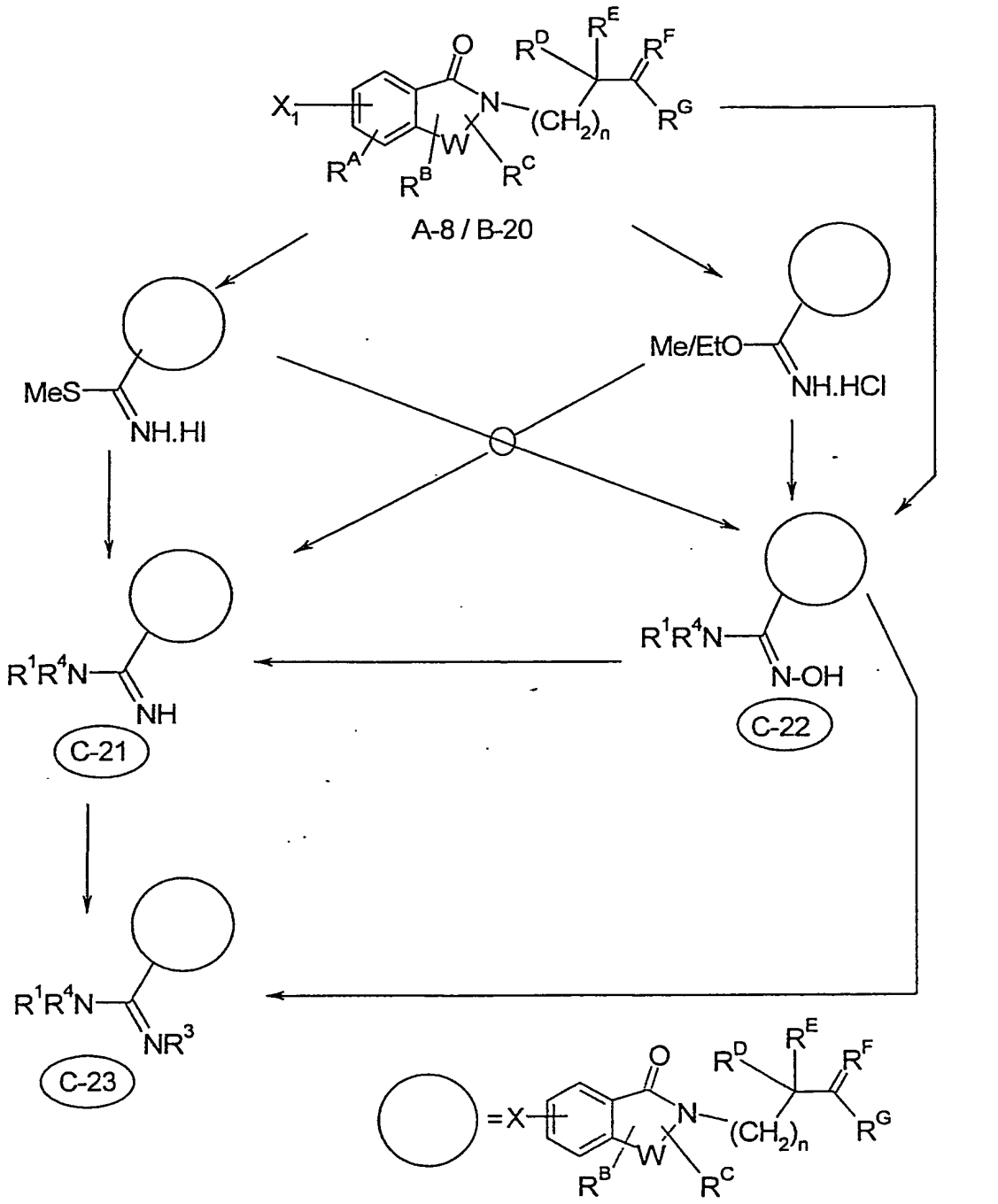

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Figure D

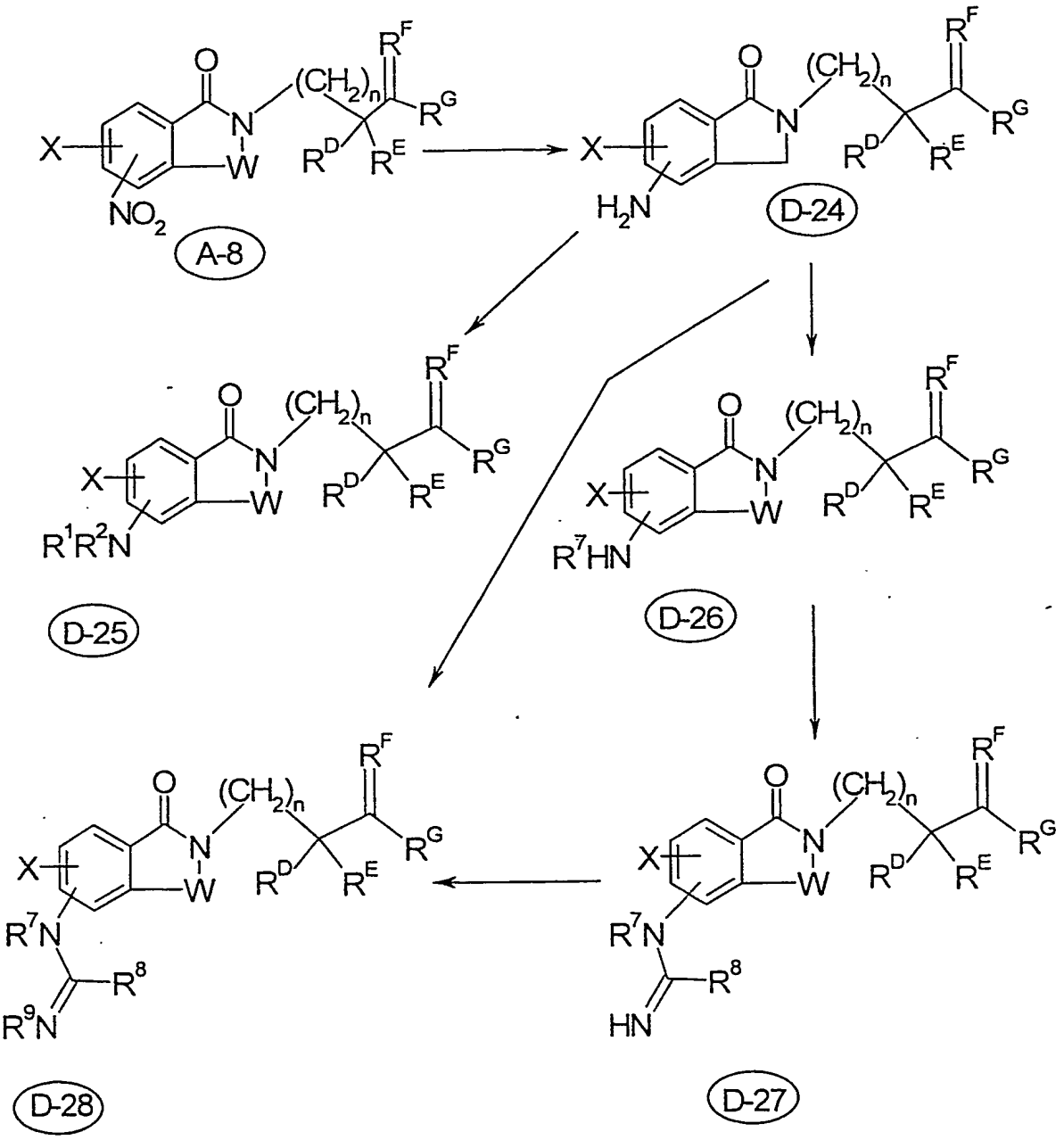

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Figure E

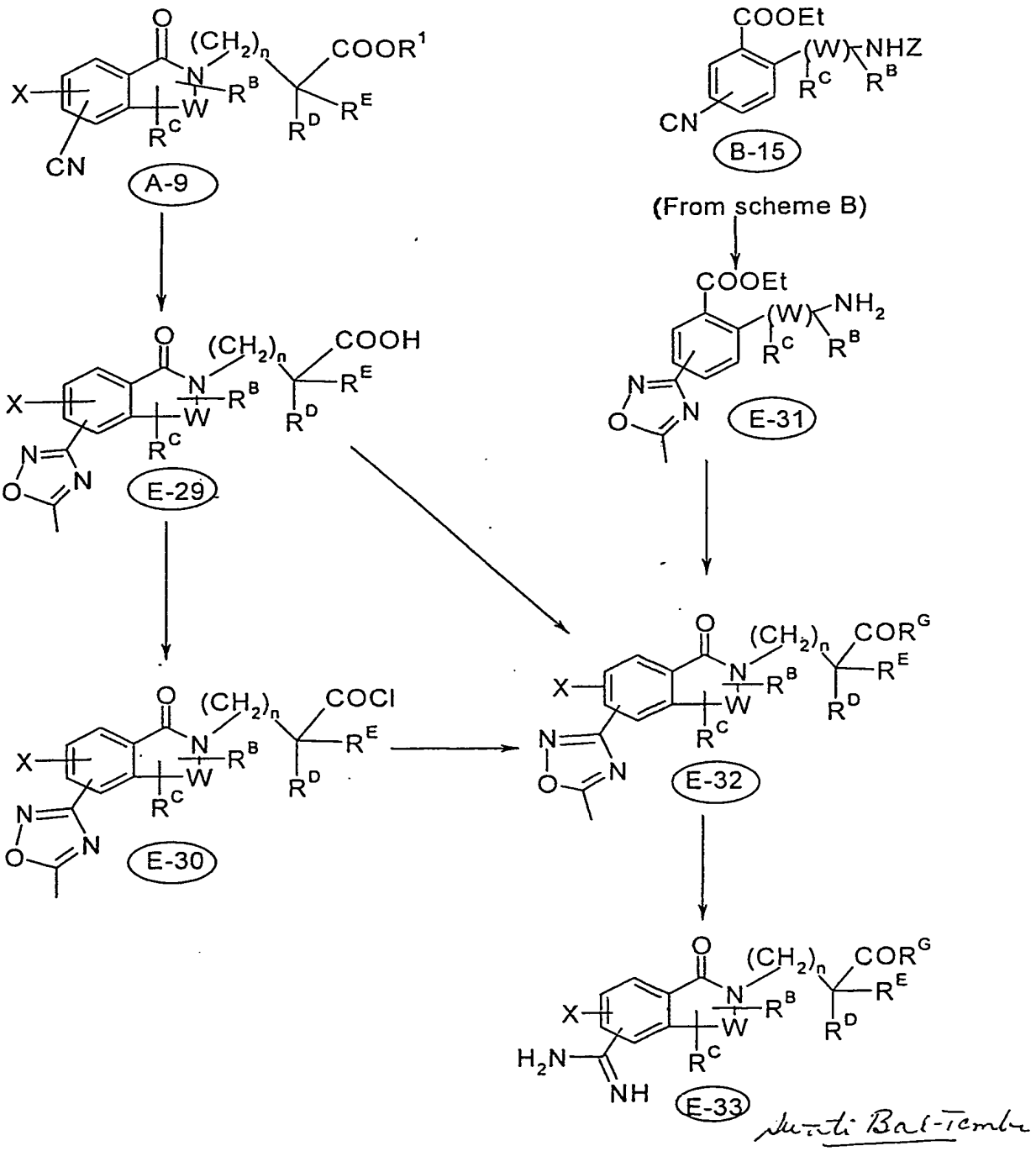

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Figure F

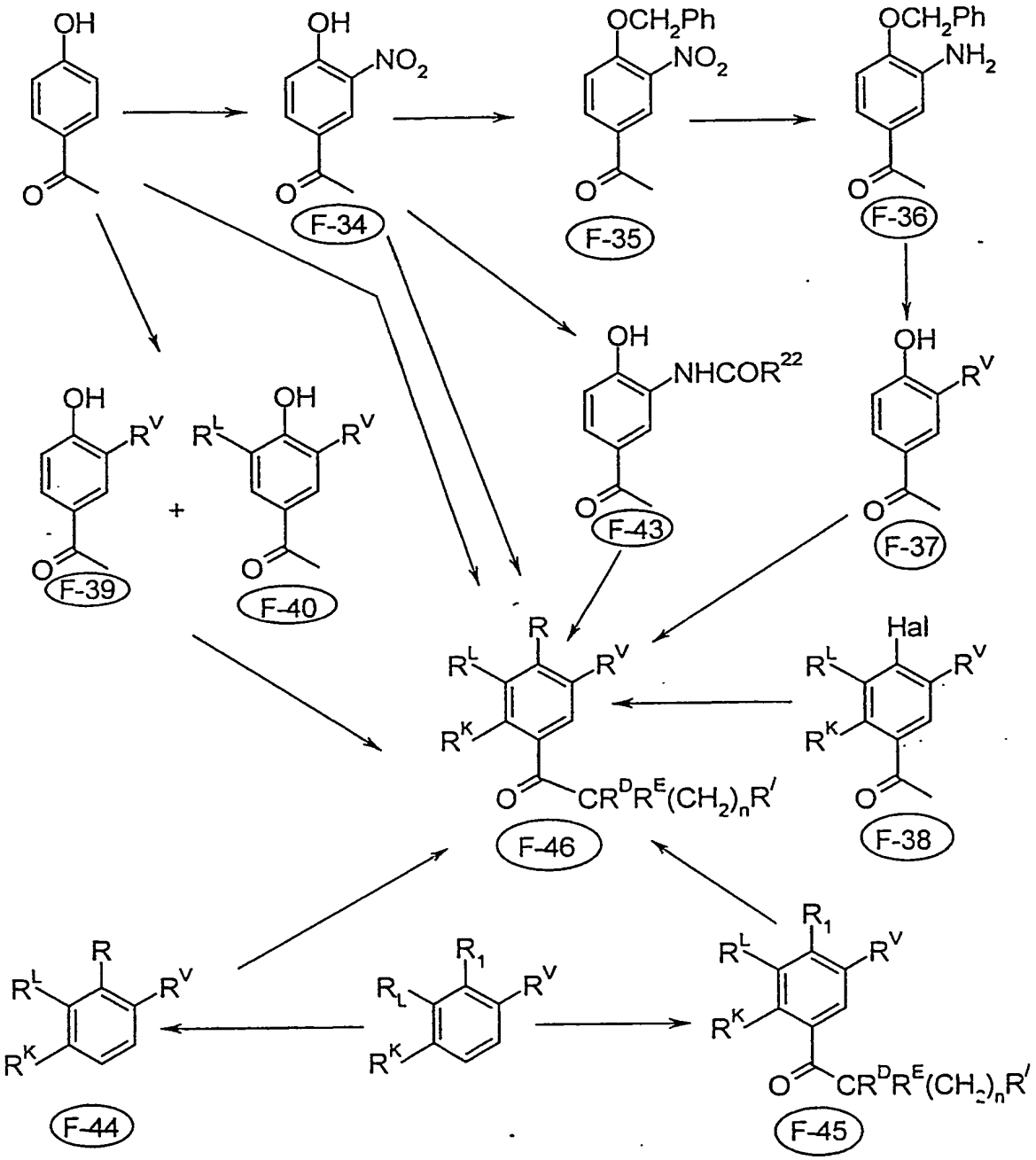

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Figure G

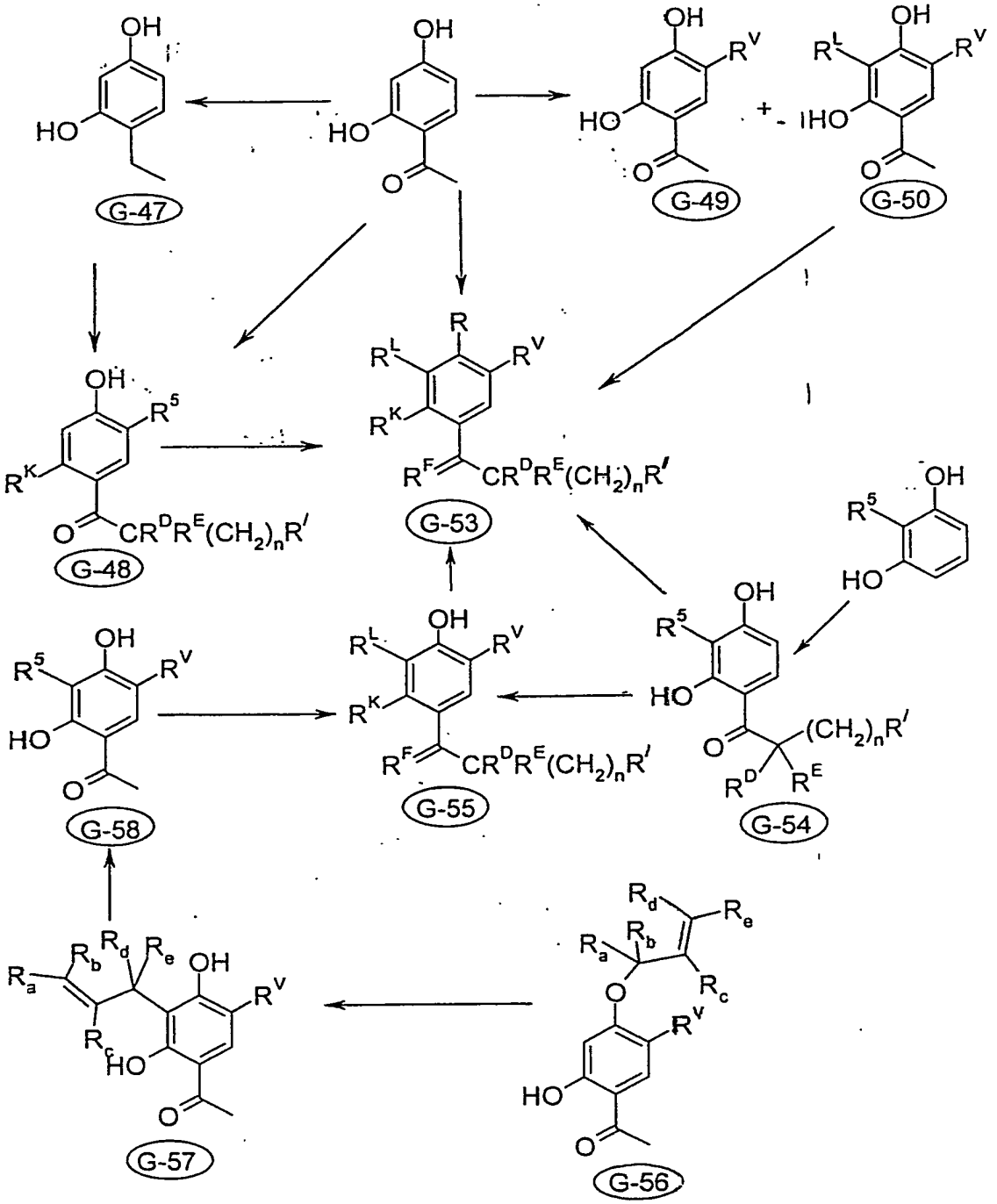

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Figure H

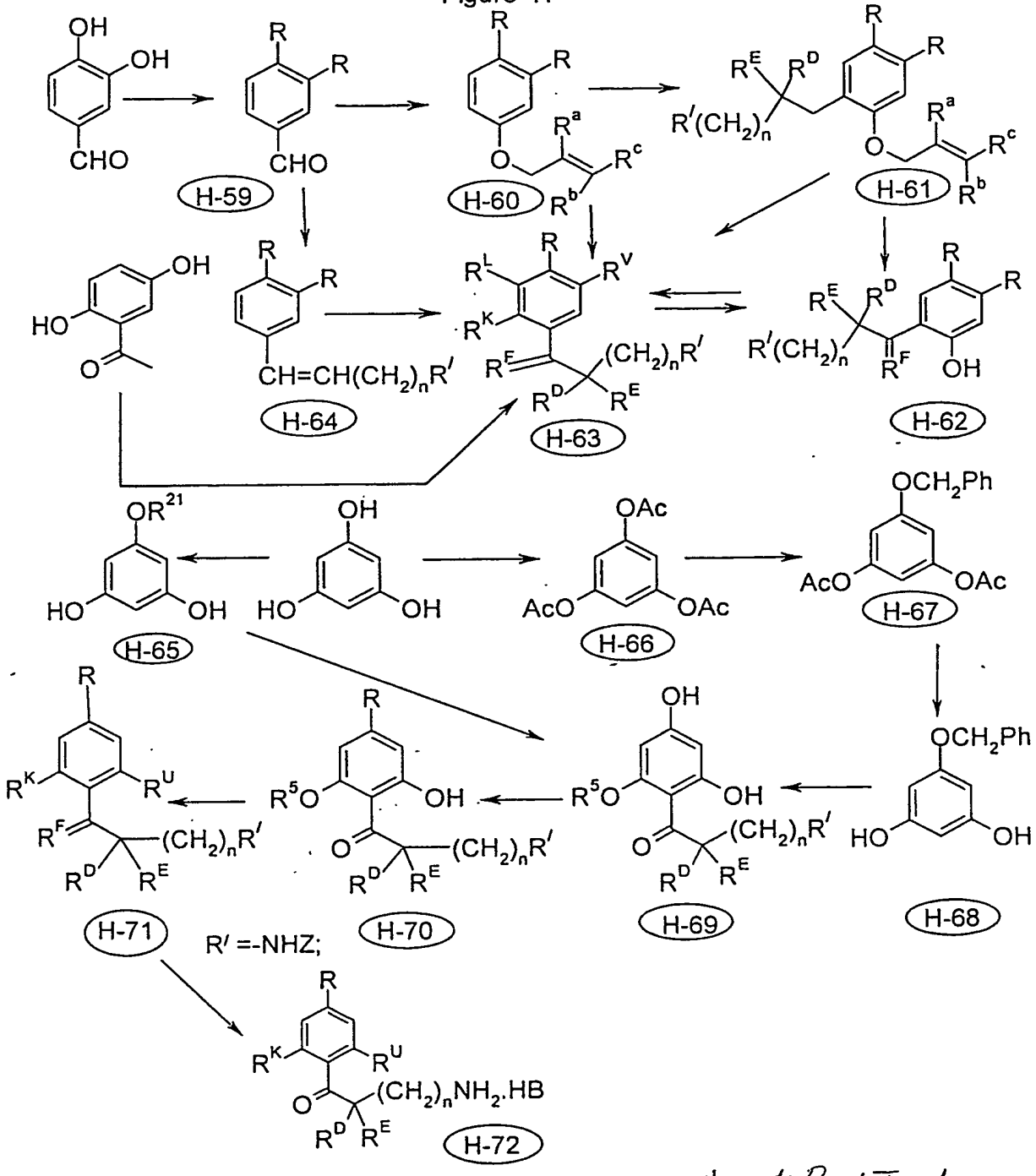

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Figure J

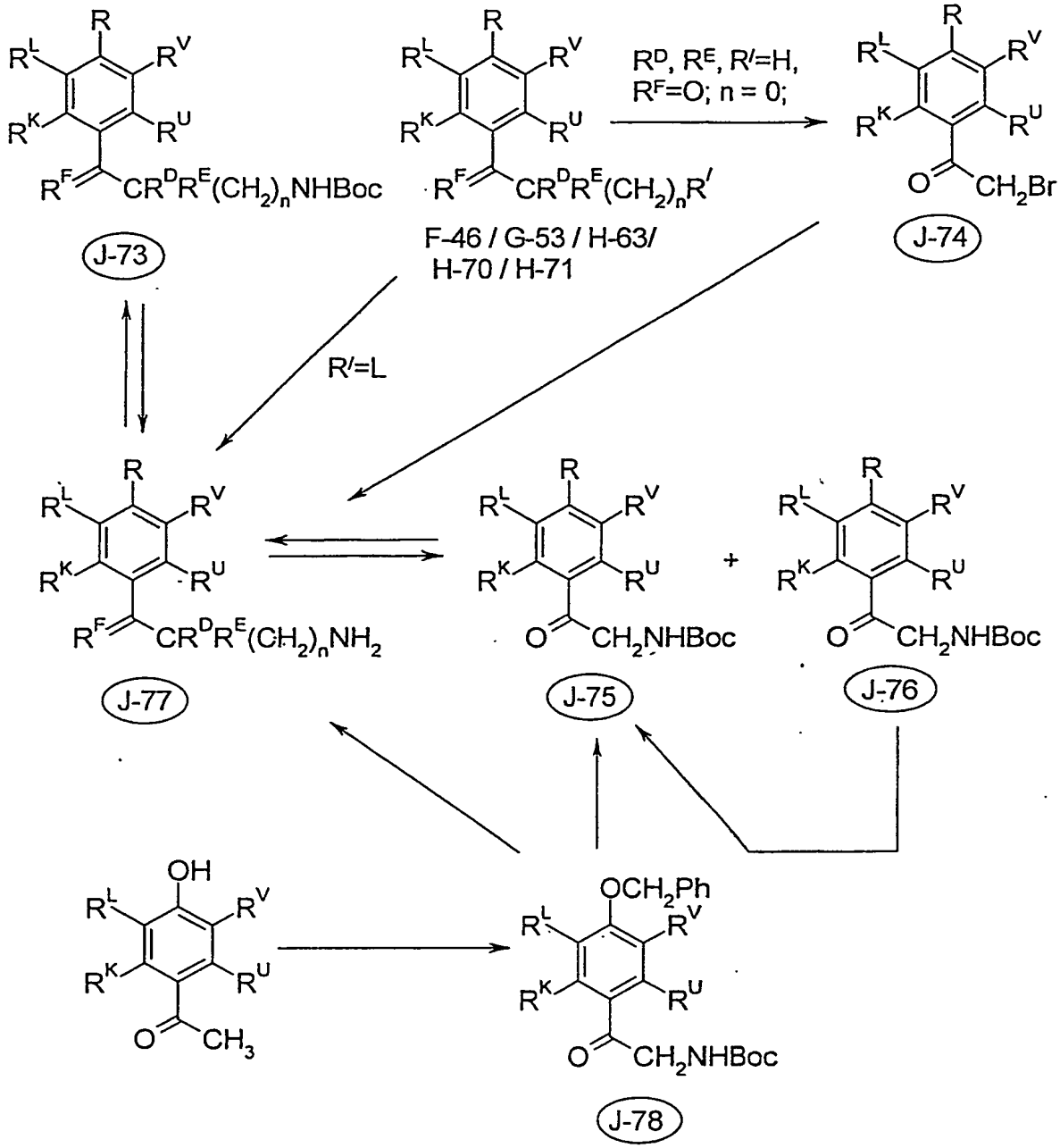

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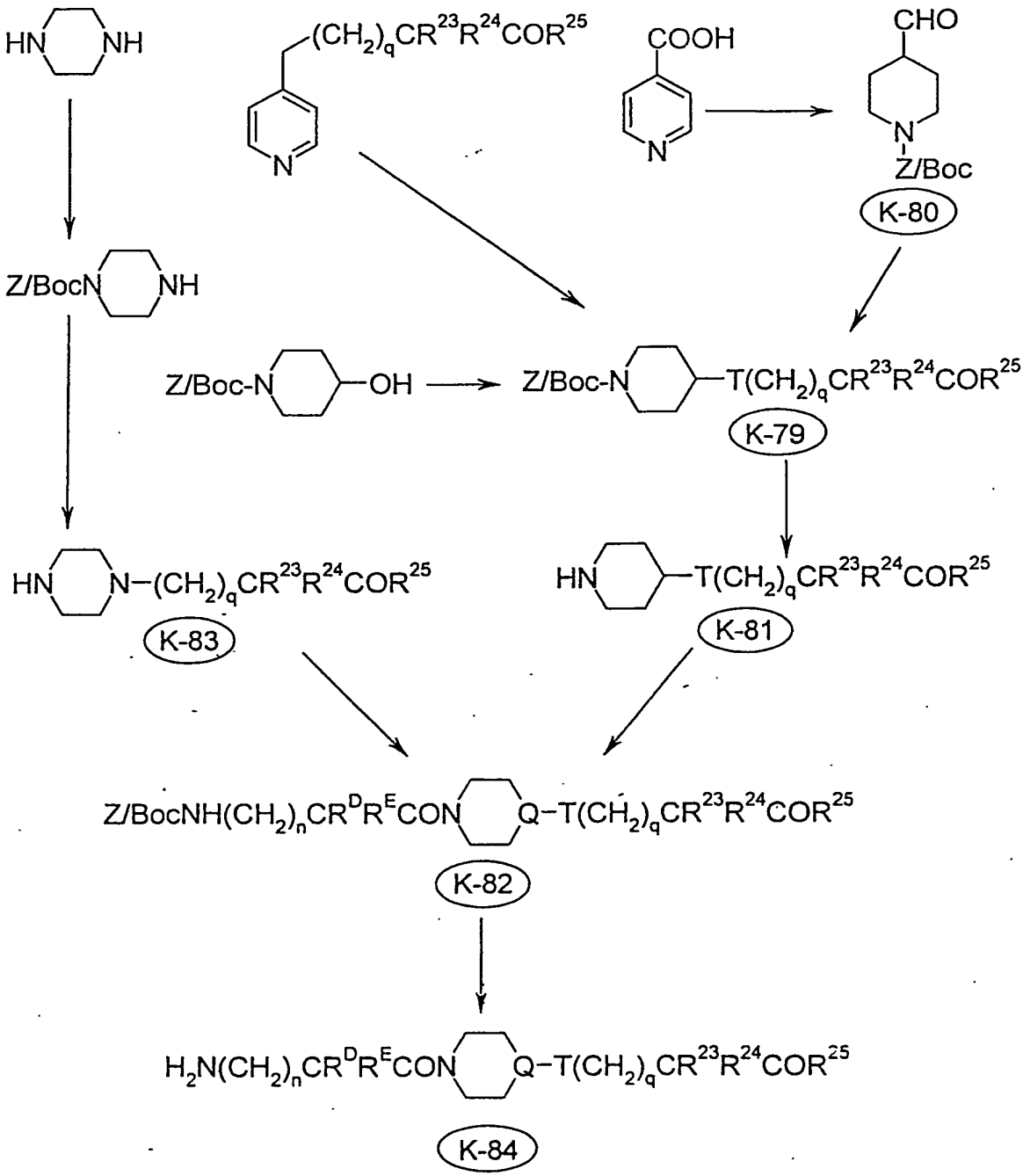
Figure K



Dr. Swati Bal-Tembe
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